CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203202Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA BIOPHARMACEUTICS REVIEW MEMO

NDA#:	203202 (N-000)
Submission Date:	07/03/13
Brand Name:	Northera
Generic Name:	Droxidopa
Formulation:	Immediate release (IR) capsules
Strength:	100, 200, and 300 mg (three strengths)
Applicant:	Chelsea Therapeutics
Type of submission:	Resubmission (6 months)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Droxidopa is reportedly an orally administered, synthetic catecholamine acid pro-drug. It had been approved in Japan since 1989 for the treatment of OH (orthostatic hypotension), syncope, and dizziness on standing up in Familial Amyloid Polyneuropathy (FAP) and Shy-Drager Syndrome, and for the treatment of freezing phenomenon and dizziness on standing up in PD (Parkinson's disease).

On 09/23/11, Chelsea submitted original NDA 203202 (N-000) for Northera (Droxidopa) 100, 200, and 300 mg IR capsules. It was designated for a priority review (6 months), but the NDA was deemed not approvable at that time. A complete response (CR) letter was sent to the Applicant on 03/28/12.

On 03/20/13, a Type A meeting was held between the Applicant and FDA to discuss the resubmission and the issues listed in the CR letter on CMC stability, Clinpharm BE study, and Clinical safety which needed to be addressed. Please see 03/28/12 CR letter and 03/20/13 MM for details. On 07/03/13, the Applicant resubmitted the NDA. The PDUFA review clock started on 08/13/13 and its goal date is 02/13/14.

From the Biopharmaceutics perspective, since the Applicant accepted the Biopharmaceutics proposed revisions to the dissolution acceptance criterion, the original NDA was accepted and recommended for approval. No further Biopharmaceutics issues are pending. Please see Biopharmaceutics review dated 01/13/12 in DARRTS for details.

Biopharmaceutics Review

No further Biopharmaceutics review is needed.

_____ 12/24/13

Tien-Mien Chen, Ph.D. Date

ONDQA Biopharmaceutics Reviewer

_____ 12/24/13

John Duan Ph.D. Date

ONDQA Biopharmaceutics Acting Team Leader

CC: NDA, Tien-Mien Chen\NDA203202 Resubmission\RLostritto

Reference ID: 3427954

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/s/

TIEN MIEN CHEN
12/24/2013

JOHN Z DUAN
12/24/2013

CLINICAL PHARMACOLOGY REVIEW

NDA:	203202
Submission Date:	08/14/2013
Submission Type:	NME, Re-submission, Priority Review
Brand Name:	NORTHERA®
Generic Name:	Droxidopa
Dosage Form & Strengths:	Capsules: 100, 200 and 300 mg
Proposed Indication:	For the treatment of symptomatic neurogenic orthostatic hypotension in adult patients with primary autonomic failure (Parkinson's Disease, Multiple System Atrophy and Pure Autonomic failure), Dopamine Beta Hydroxylase Deficiency and Non-Diabetic Autonomic Neuropathy
Applicant:	Chelsea Therapeutics
Review Divisions:	DCRP & DCP1
Primary Reviewer:	Sreedharan Sabarinath, Ph.D.
Team Leaders:	Yaning Wang, Ph.D. Rajanikanth Madabushi, Ph.D.

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EXECUTIVE SUMMARY

Chelsea Therapeutics, Inc. had an original new drug application (NDA 203-202, submission date 09/03/2011) for droxidopa capsules for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in adult patients with primary autonomic failure (Parkinson's disease, Multiple System Atrophy and Pure Autonomic Failure), Dopamine Beta Hydroxylase Deficiency and Non-Diabetic Autonomic Neuropathy. This original NDA received a complete response (CR) after a priority review and an advisory committee meeting (CR letter date 03/28/2012). Original clinical pharmacology question based review (QBR) and individual study reviews were completed in the first review cycle and are available in DARRTS (dates 01/25/2012 and 03/18/2012). The current re-submission includes one pivotal efficacy study (306B) and a bioequivalence study (104) for a new 300 mg capsule strength.

The pivotal efficacy study 306B was in adult patients with symptomatic neurogenic orthostatic hypotension (NOH) associated with Parkinson's disease and had parallel treatment arms with droxidopa and matching placebo with an initial double-blind dose-titration phase followed by an 8-week maintenance phase. Study 306B showed a treatment effect of 1.0 unit (p=0.018) favoring droxidopa for the primary efficacy endpoint (placebo adjusted change from baseline to week 1 for Orthostatic Hypotension Symptom Assessment, OHSA, Item-1).

In order to reduce the pill burden the applicant is planning to market a new 300 mg strength capsule. The 200 mg and 100 mg capsules were used in Phase III and the applicant has performed a pivotal bioequivalence (BE) study using one 300 mg capsules (test) and a combination of one 100 mg capsule and one 200 mg capsule (reference).

The current review focuses on:

- Exploratory dose-response analyses for droxidopa for NOH symptom relief and blood pressure (BP), and
- Pivotal BE study for the 300 mg capsule strength

1.1 Summary of OCP Findings

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology and biopharmaceutics (CPB) information provided in the NDA 203-202 and our observations are listed below:

- NOH is an orphan indication with limited treatment options and one might find some clinical utility in approving droxidopa for short term symptom relief. But the pattern of symptom relief based on CGI-S was comparable for both droxidopa and placebo groups

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during the dose-titration phase. The observed intra-individual variability (~ 2.9 units) for OHSA Item-1 is much higher than the treatment effect of 1.0 unit favoring droxidopa and the treatment effect lost statistical significance after one week.

- The bioequivalence (BE) result from Study 104 is acceptable. However, the clinical and bioanalytical site inspection report from Office of Scientific Investigations (OSI) for this pivotal BE study is currently pending. The approvability of the 300 mg capsule strength depends on the findings from OSI.

1.2 Post Marketing Requirements/Commitments

The OCP review dated 01/25/2012 included a PMR for conducting a dedicated renal impairment study for droxidopa. The applicant had an active study protocol for this study at that time and was expected to submit the report post-approval during the first review cycle. However, the study was not completed after receiving complete response and the PMR from our prior review is still applicable.

Background of Efficacy Study 306

The initial objective of the phase III study 306 was to measure the durability of treatment effects with droxidopa. The change from baseline in orthostatic hypotension questionnaire (OHQ) composite score at week-8 was the original primary efficacy endpoint. However, after an interim analysis when about 60 % of enrolled patients either completed end of study visit or lost to follow-up, the applicant modified the study 306 by dividing it into two parts, 306A and 306B. Patients who were included in the interim analysis were grouped as study 306A and patients enrolled after the interim analysis and those patients who were not included in the interim analysis were considered as part of Study 306B. There were a total of 171 patients enrolled in study 306B, with 87 patients on droxidopa and 84 patients on placebo respectively. The original intent was to measure reduction in patient reported falls as the primary efficacy endpoint. But the statistical analysis plan (SAP) was changed prior to completion of 306B and the protocol amended to have change in Orthostatic Hypotension Symptom Assessment (OHSA) Item-1 (dizziness/light headedness) from baseline to week-1 after the dose titration phase (Visit 4, See Figure 1 below) as the primary efficacy endpoint. The study 306B is considered as the pivotal efficacy trial for this re-submission. Unlike the prior efficacy trials reported in the original submission (Studies 301 or 302), the study 306 included only Parkinson's patients with symptomatic neurogenic orthostatic hypotension (NOH).

2.1 Design of Study 306B

This was a multi-center, placebo-controlled, parallel-group, double-bind Phase III study in adult patients with symptomatic NOH associated with Parkinson's disease. The design features of Study 306B is shown in Figure 1. After screening for eligibility and at the end of the baseline visit (Visit 2) all eligible patients (~171) were randomized in a 1:1 ratio to treatment with either droxidopa or placebo. The patients then entered a double-blind dose-titration phase at 100 mg three times daily (TID) of droxidopa or matching placebo. Treatment was escalated in 100 mg TID increments until one of the following titration stopping criteria was met.

1. Patients becoming completely asymptomatic for NOH as reported on clinician recorded Clinical Global Impression score for severity (CGI-S). The CGI-S scores range from 1 to 7 and a score of 1 is considered normal or no NOH symptoms. The titration may also have been stopped when a patient became nearly asymptomatic (e.g. CGI-S score of 2, borderline NOH) in clinician's opinion, or

2. Patient's systolic blood pressure (BP) ≥ 180 mm Hg or diastolic BP ≥ 110 mm Hg after 10 minutes in supine position (with head and torso elevated at 30° from horizontal). The titration can also be stopped if the BP was close to the limits if necessary, or

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3. Patient cannot tolerate the side effects with a dose, or

4. Patient reached the maximum allowed dose of 600 mg TID.

A patient can proceed directly to the 8-week double-blind maintenance phase at that dose after meeting criterion-1 at any stage of the dose titration. Patients who met criteria 2 or 3 can advance to the maintenance phase at the previous (one step lower) dose, except for those at the starting dose of 100 mg TID because they will be withdrawn from treatment. Patients who met criterion-4 can continue to the maintenance phase on 600 mg TID as their selected dose. The dose titration will be for up to 2-weeks depending on the number of titration steps involved (maximum 6 steps).

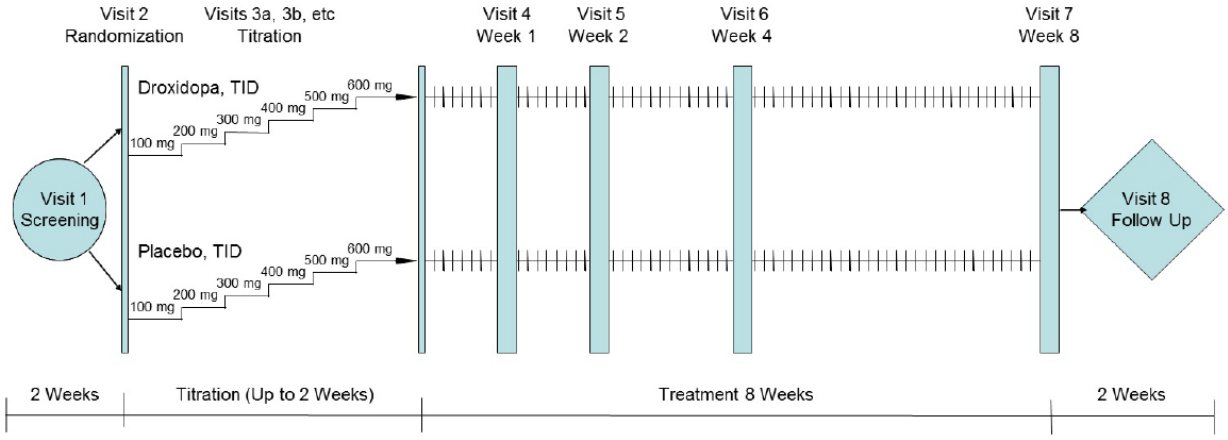

Figure 1. Design of study 306B in NOH patients with Parkinson's disease. There is a 2-week double-blind dose-titration phase, followed by 8-week double-blind maintenance phase. A total of 171 patients were enrolled in to this study (87 patients on droxidopa and 84 patients on placebo treatment groups respectively). The primary efficacy analysis was at week-1 (Visit 4) after the titration phase. *Ref: Figure 9-1 from Clinical Study Report, Page 22. \\cdsesub1\evsprod\NDA203202\0048\m5\53-clin-stud-rep\535-rep-effic-safety-stud\noh-symptoms\5351-stud-rep-contr\noh306b*

During the maintenance phase patients returned for study visits after 1, 2, 4 and 8 weeks of double-blind treatment (Visits 4, 5, 6 and 7 respectively). The CGI-S and orthostatic standing test (OST) for BP measurements were taken during each titration visits and maintenance visits. The OHQ composite, which includes OHSA and OHDAS scores, was done only at baseline and visits during the maintenance phase. Details of the patient reported outcome instruments used this study are described in detail previously (Ref. SEALD endpoint review by Dr. Elektra Papadopoulos DARRTS date 01/24/2012).

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2.2 Efficacy Results

The primary efficacy endpoint for study 306B was mean change in OHSA Item-1 (dizziness/light headedness) from baseline to week-1 (visit 4) for the full analysis set (FAS). The FAS was mITT with all randomized patients who received at least one dose of study treatment and have reported OHSA Iten-1 at week-1. Of the 174 randomized patients, 171 patients received at least one dose of treatment (ITT) and 147 patients were included in FAS (N=78 on placebo and N=69 on droxidopa). Demographics and baseline NOH disease severity were similar between placebo and treatment groups. Study 306B showed a treatment effect of 1.0 (p=0.018) on OHSA Item-1 from baseline to week-1 favoring droxidopa (See Table 1 below). However, the observed intra-individual variability for OHSA Item-1 was 2.9 units on 11 point scale (Ref. Statistical Review by Dr. Jialu Zhang, DARRTS date 12/04/2013).

Table 1. Average OHSA Item-1 Scores from Study 306B

Visits/Treatment	Placebo	Droxidopa
Baseline (Randomization)	5.1 (2.3), N=78	5.1 (2.0), N=69
Week-1 (Visit-4)	3.8 (2.8), N=78	2.8 (2.4), N=69
Week-2 (Visit-5)	3.3 (2.3), N=75	3.3 (2.7), N=68
Week-4 (Visit-6)	3.6 (2.6), N=73	2.1 (2.6), N=67
Week -8 (Visit-7)	3.6 (2.6), N=68	3.0 (2.8), N=63

OHSA Item-1 values are Mean (SD), FAS for week-1. Primary efficacy analysis is at week 1 and excluded patients who discontinued prior to week-1.

The change from baseline on SBP during OST also favored droxidopa group at week-1 (an improvement of about 6.4 mm Hg on droxidopa versus 0.7 mm Hg on placebo for the lowest SBP recorded from +0 to +3 minutes on OST). There were more discontinuations prior to week-1 in the droxidopa group (N=18) compared with the placebo group (N=6) and were thought to be discontinuations related to adverse events. The secondary efficacy variables included mean change in OHSA Item-1 from baseline to weeks-2, 4 and 8. The observed difference from placebo were -0.2 (p=0.6), -0.5 (p=0.308) and -0.6 (p=0.187) at weeks-2, 4 and 8 respectively for droxidopa treatment.

2.3 Exploratory Dose-Response Analyses

Previous Phase III studies (301 and 302) had open label dose-titration with only droxidopa (and no placebo) and our analyses reported in the previous review may have been confounded by the placebo response over time. Also, the dose-escalation criteria in those trials were different (based on OHSA Item-1 and BP while 306B used CGI-S mainly). The double-blind, parallel group design of study 306B provided a direct comparison between droxidopa and placebo.

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In study 306B, the distribution of doses on droxidopa and placebo groups were almost comparable (Figure 2) with about 40 % and 48 % of patients requiring the maximum dose of 600 mg TID for droxidopa and placebo respectively, while about 7-8 % of patients remained with the lowest dose of 100 mg TID on both treatment groups.

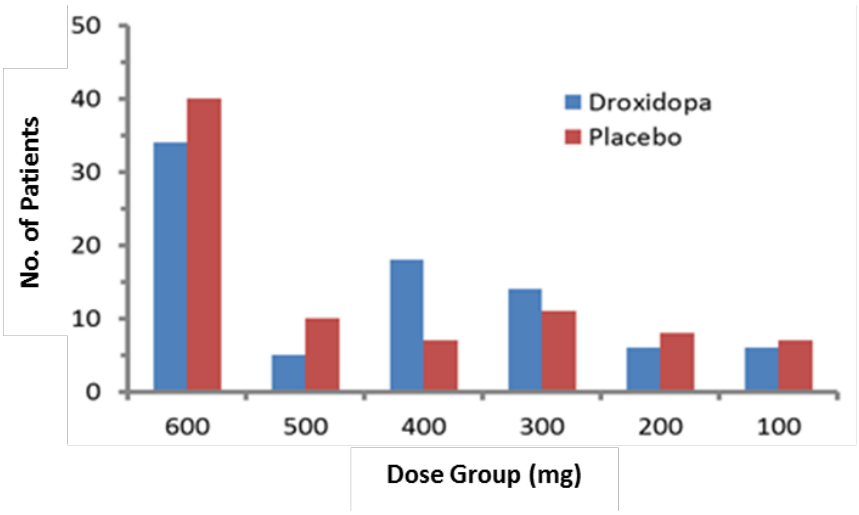


Figure 2. Distribution of doses in the droxidopa and placebo treatment groups. Assigned dose information from dataset ADCGI.xpt

The clinician reported CGI-S was used for dose escalation (not OHSA Item-1) and CGI-S was the only measure for symptom relief available during the titration phase. Lowest standing SBP from OST is a hemodynamic measure related to NOH condition and OSTs were performed after CGI-S assessments in each patient. Therefore, exploratory dose-response analyses were carried out for both droxidopa and placebo patients for CGI-S and lowest standing SBP from OST.

The symptom relief, as measured with clinician reported CGI-S showed a similar pattern for both droxidopa and placebo treatments during dose-titration. This was also evident from the comparable distribution of doses in the droxidopa and placebo groups. Since CGI-S was also reported during the maintenance visits it was possible to evaluate the durability of treatment effects on droxidopa and placebo (Figure 3A and 3B) and the treatment effects generally declined over time. This was in agreement with the observation that primary efficacy variable OHSA Item-1 also declined over time and lost statistical significance after week-1 (Visit-4).

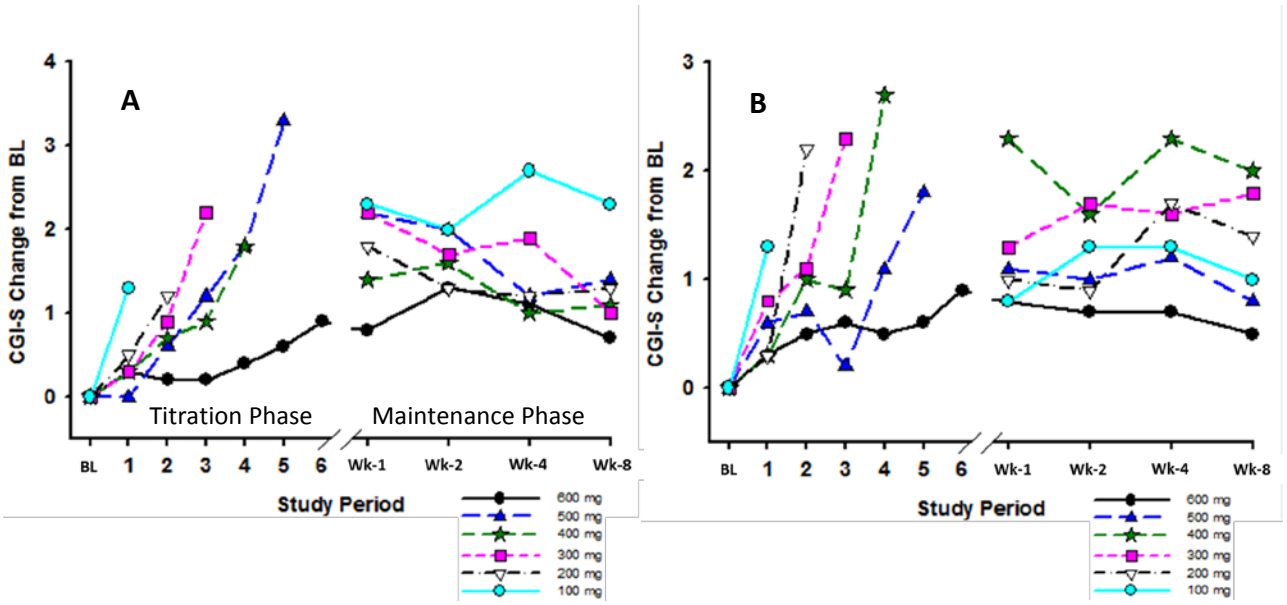


Figure 3. Mean improvement from baseline for clinician reported CGI-S scores during the double-blind dose-titration phase and 8-week maintenance phase with **droxidopa (A)** and **placebo (B)**. Each line represents a maintenance dose group as patients are dose-titrated, starting with 100 mg TID on the first day to a maximum dose of 600 mg TID. BL stands for baseline and there are 6 possible dose titration steps. For example, patients who had 600 mg TID as their individualized dose went through all 6 dose titration steps, 100, 200, 300, 400, and 500 mg TID before reaching their optimal dose of 600 mg TID, whereas patients who had 100 mg TID as their individualized dose did not have any other dose level. See dose titration criteria for details. The X-axis break denotes the transition from dose-titration phase to maintenance phase. Data source: ADCGI.xpt

As per the proposed mechanism of action of droxidopa (that it shows pharmacological effects by releasing norepinephrine) a dose dependent effect on BP was expected. But there were no clear dose dependent effects on SBP with droxidopa treatment (Figure 4A) probably because the dose-escalation was based on symptom relief (CGI-S) and not on BP. The placebo treatment did not show any dose dependent effects on SBP unlike the symptom relief seen on CGI-S (Figure 4B).

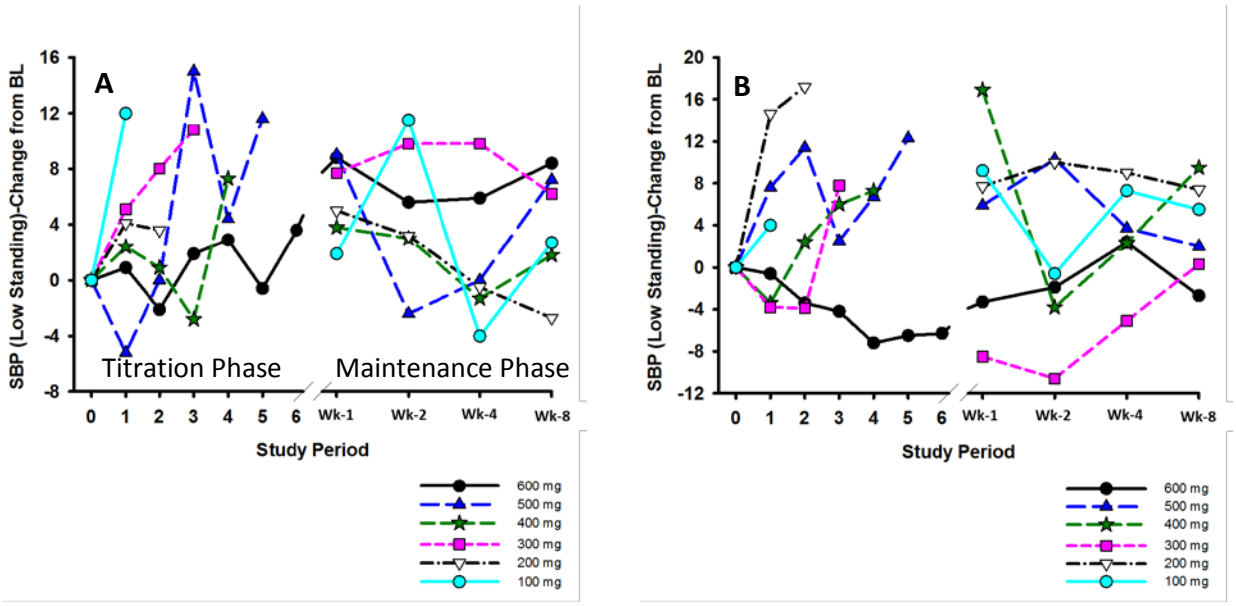


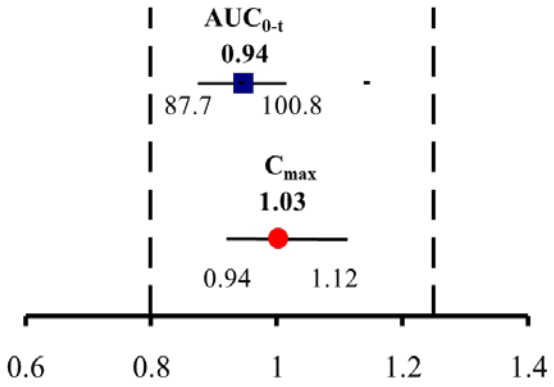
Figure 4. Mean change from baseline for lowest standing systolic BP (mm Hg) from OST during the double-blind dose-titration phase and 8-week maintenance phase with **droxidopa (A)** and **placebo (B)**. Each line represents a maintenance dose group as patients are dose-titrated, starting with 100 mg TID on the first day to a maximum dose of 600 mg TID. Data source: ADORTH.xpt

2.4 Observations from Study 306B

- Study 306B showed a statistically significant treatment effect of 1 unit difference on OHSA Item-1 (on a 11 point scale) favoring droxidopa over placebo
- Clinical significance of the observed treatment effect of 1 unit for OHSA Item-1 is not well understood. The observed intra-individual variability is ~ 2.9 units for OHSA Item-1.
- There was significant placebo response for NOH symptom relief as evident from clinician reported CGI-S scores during dose-titration.
- The observed, statistically significant treatment effect for OHSA Item-1with droxidopa was sustained only for a week during the maintenance phase. The treatment effect generally declined and lost statistical significance during the 8-week maintenance phase.

Pivotal BE Study

Study No. 104 Study Period: 2013	**Title:** A Randomized, Open-Label, Bioequivalence Study of one 100 mg and one 200 mg Capsule of Droxidopa versus one 300 mg Capsule of Droxidopa in Healthy Subjects
EDR Link:	\\cdsesub1\evsprod\NDA203202\0044\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\noh104
Primary Objective: To demonstrate bioequivalence (BE) of one 100 mg capsule and one 200 mg capsule of droxidopa versus one 300 mg capsule of droxidopa in healthy subjects	
Study Design: Open-label, randomized, 2-period, 2-treatment, single-dose, cross-over study Reference Treatment: One 100 mg, Lot # HSDC and one 200 mg capsule, Lot # HSDG (Treatment A) Test Treatment: One 300 mg capsule, Lot # KSPB (Treatment B) Note: Subjects fasted overnight, single dose test/reference treatment was administered with 240 ml water and the first meal was 4 hours after dosing. A 3-day wash-out period was used between treatments.	
Study Population: Healthy adult male/female subjects (N=24), 18-65 years of age with BMI 18-35 kg/cm^2. Women should not be nursing or pregnant.	
Analytical Method: Validated LC-MS/MS method for used for quantifying droxidopa from blood plasma. Calibration range 5-3000 ng/ml.	
PK Sampling: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h post dose	
Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90 % CI for the difference were constructed.	
Results: The figure below shows the ratio of LS means of test divided by reference treatments for primary PK parameters and their 90 % confidence intervals (N=24). Dotted vertical lines shows the BE lower and upper limits of 0.8 and 1.25 respectively.	



The observed median t_{max} for droxidopa was 3 hours for both test and reference treatments. There were no deaths, serious adverse events or discontinuations due to an adverse event in this study.

Site Inspection: A clinical and bioanalytical site inspection is being conducted by OSI and the inspection report is currently pending.

Reviewer's Comments:

- *The 300 mg capsule is bioequivalent to a combination of one 100 mg capsule and one 200 mg capsule. However, the approvability of the 300 mg strength depends on the OSI inspection report.*

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/s/

SREEDHARAN N SABARINATH
12/05/2013

YANING WANG
12/05/2013

RAJANIKANTH MADABUSHI
12/05/2013

CLINICAL PHARMACOLOGY REVIEW ADDENDUM
INDIVIDUAL STUDY REVIEWS

NDA	203-202
Submission Date	09/23/2011
Submission Type	Original NDA (NME – Priority Review)
Brand Name	Northera®
Generic Name	Droxidopa
Dosage Form & Strength	Oral capsules (100, 200 and 300 mg)
Indication	Treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure, dopamine β-hydroxylase deficiency and non-diabetic autonomic neuropathy.
Applicant	Chelsea Therapeutics, Inc
Review Division	DCP1 & DCRP
Primary Reviewer	Sreedharan Sabarinath, PhD
Pharmacometrics	Fang Li, PhD & Sreedharan Sabarinath, PhD
Pharmacometrics Team Leader	Yaning Wang, PhD
Pharmacogenomics	Hobart Rogers, Pharm D, PhD
Pharmacogenomics Team Leader	Michael Pacanowski, Pharm D, PhD
OCP Team Leader	Rajanikanth Madabushi, PhD
Dosage Form & Strength	Oral capsules (100, 200 and 300 mg)

This is an addendum to the clinical pharmacology question based review (QBR) for NDA 203-202 droxidopa (Northera®), finalized in DARRTS on 01/25/2012. Studies that were mentioned in the above referenced QBR but not described in detail are included in this review**.**

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1. CLINICAL PHARMACOLOGY STUDY REVIEWS

1.1 BIOANALYTICAL METHODS

Two validated LC-MS/MS methods ((b) (4) method and (b) (4) method) were used for the estimation of droxidopa and its metabolites methylated droxidopa (3-OM-DOPS) and norepinephrine (NE). Both methods were validated for these analytes in human plasma.

Linearity ranges for the analytical methods used

Analyte	(b) (4) Method*	(b) (4) Method**
Droxidopa	5 – 3000 ng/mL	50 – 10,000 ng/mL
3-OM-DOPS	5 – 3000 ng/mL	10 – 600 ng/mL
NE	50 – 2500 pg/mL	20 – 2500 pg/mL

*For studies 101, 102 and 302, **For studies 20-1859-94 and 20-1860-94

The accuracy and precision of the assay methods were within limits (≤20% at LLOQ and ≤15% at all other QC levels) and the validation parameters reported for these two methods are acceptable.

1.2 IN VITRO STUDIES

1.2.1 Protein Binding

Study No. D-07	**Protein binding of L-DOPS**
EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m4\42-stud-rep\422-pk\4223-distrib\d-7	
Objectives: To investigate the protein binding of L-DOPS (droxidopa) and 3-OM-DOPS in human and animal serum	
Study Design: Protein binding was measured using *in vitro* equilibrium dialysis using multi-well equilibrium dialysis cell and incubation was carried out for 18 hours. The concentration range tested was 0.1 to 10 ug/mL for droxidopa. 3-OM-DOPS was tested at a concentration of 1 ug/mL.	
Results: Serum protein binding of droxidopa at 0.1, 1 and 10 ug/mL concentrations were 75.4 %, 50.1 % and 26.2 % respectively. Serum protein binding of 3-OM-DOPS was 1.02%.	
Comments: • The concentration range studied for droxidopa covers the exposure in humans with therapeutic doses. The protein binding of droxidopa in human serum was moderate and concentration dependent. However, it is not clear if the equilibration time used in the study was adequate for all concentration levels. • 3-OM-DOPS showed low serum protein binding in humans	

Reference ID: 3101864

1.2.2 CYP inhibition

Study No. ZNA31751.001	**Investigation of the Potential Inhibitory Effect of Droxidopa on Human Cytochrome P450 (CYP) Model Substrates**
EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m4\42-stud-rep\422-pk\4224-metab\zna31751-001	
Objectives: To investigate the potential inhibitory effect of droxidopa on the following human hepatic cytochrome P450 (CYP) enzyme activities: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4.	
Study Design: Direct and mechanism-based inhibitions were investigated using a pool of human liver microsomes. For the investigation of the potential direct and time-dependent inhibitory effect a range of 8 concentrations of Droxidopa, 3, 10, 30, 50, 100, 150, 200 and 300 µg/mL final concentration) were selected to cover 1- to 100-fold the maximum expected human plasma C_{max}. **Model Substrates:** phenacetin (1A2), coumarin (2A6), bupropion (2B6), amodiaquine (2C8), tolbutamide (2C9), S-mephenytoin (2C19), dextromethorphan (2D6), chlorzoxazone (2E1) and testosterone / midazolam (3A4).	
Results: **Direct Inhibition:** After incubation in the presence of 3, 10, 30, 50, 100, 150, 200 and 300 µg/mL Droxidopa an IC_{50} value for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 could not be determined as the concentration range of Droxidopa (3 to 300 µg/mL) did not cause sufficient inhibition of enzyme activity (i.e. greater than 50 %), therefore the IC_{50} is likely to be greater than 300 µg/mL. After incubation in the presence of 300 µg/mL Droxidopa, 153 %, 108 %, 90.5 %, 105 %, 99.1 %, 103 %, 145 %, 106 %, 87.2 % and 151 % remaining activity was measured for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 respectively. As inhibition of CYP model substrate activities were less than 50 %, no further evaluation was performed. **Mechanism Based Inhibition:** After incubation in the presence of 300 µg/mL Droxidopa, 107 %, 107 %, 151 %, 80.4 %, 106 %, 150 %, 182 %, 97.7 %, 102 % and 111 % vehicle activity were measured for CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 respectively. As no reliable increase of the inhibition of CYP model substrate activities was observed, no further evaluation was performed.	
Comments: Droxidopa, at the concentration range selected, is not likely to cause clinically significant inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Droxidopa has low potential for metabolic drug-drug interactions based on CYP inhibition.	

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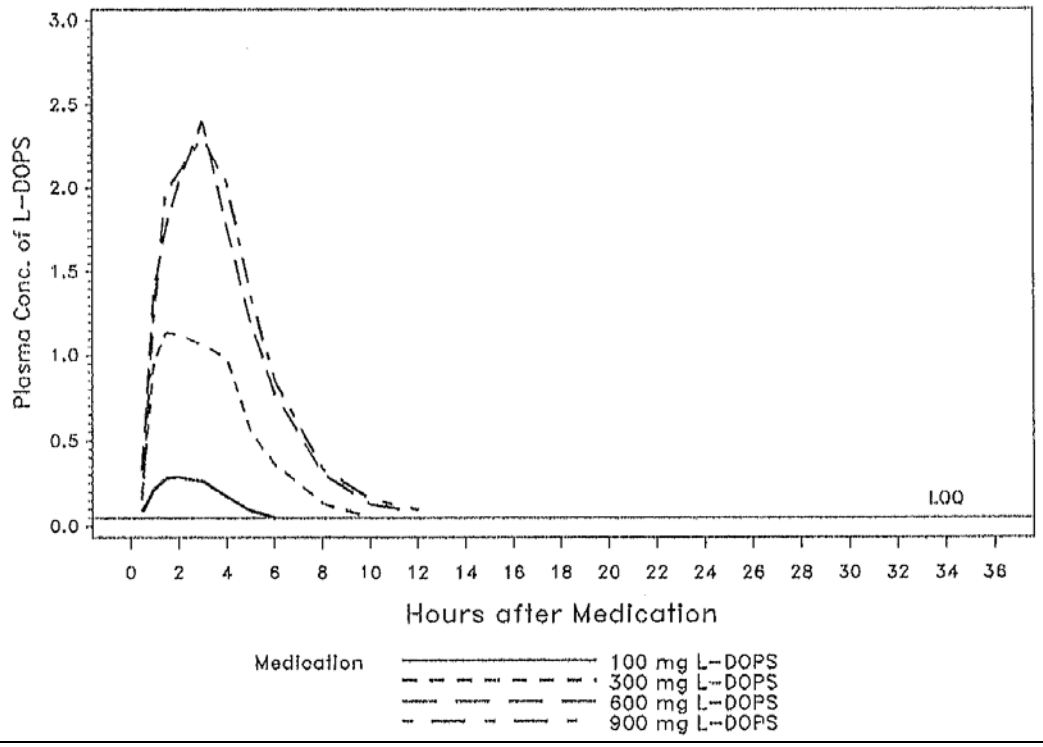
1.2.3 CYP induction

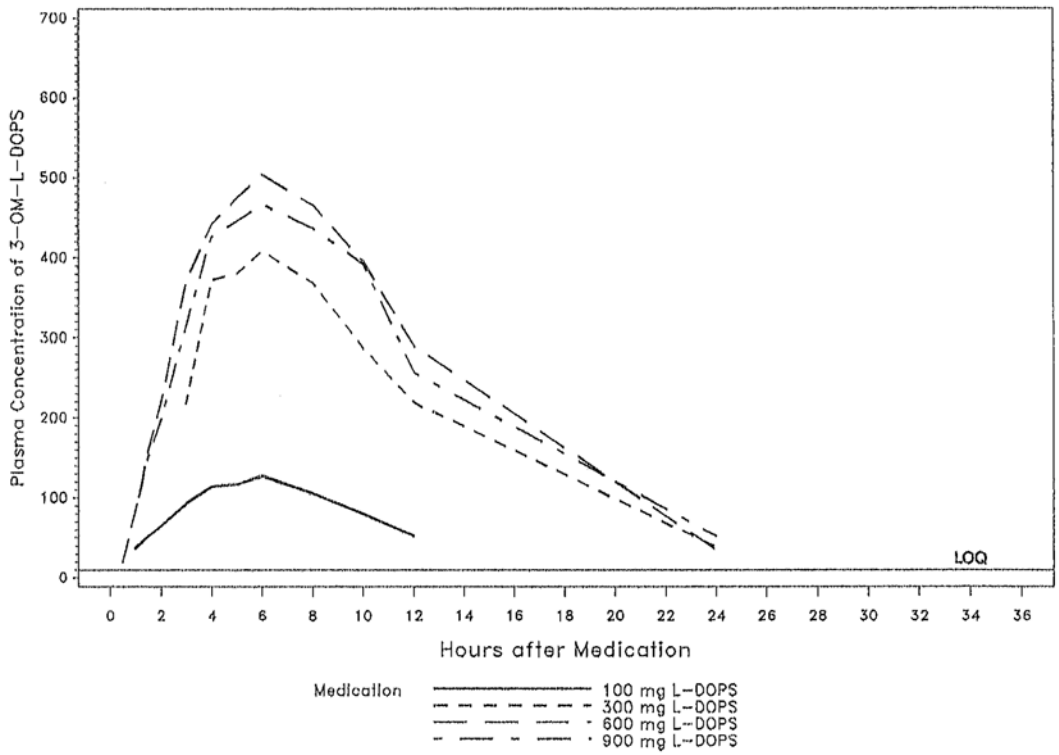
Study No. ZNA31751.002	**Evaluation of the Potential Induction Effect on Cytochrome P450 CYP1A2, CYP2B6 and CYP3A4/5 Enzyme Activities in Freshly Isolated Human Hepatocytes**
EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m4\42-stud-rep\422-pk\4224-metab\zna31751-002	
Objectives: to investigate the potential induction effect of Droxidopa on cytochrome P450 CYP1A2, CYP2B6 and CYP3A4/5 enzyme activities in fresh human hepatocytes in primary culture.	
Study Design: Model substrates: phenacetin (1A2), bupropion (2B6), and testosterone (3A4) Model inducers: omeprazole (1A2), phenobarbital (2B6) and rifampin (3A4/5) Four concentrations of droxidopa (expected C_{max} plasma concentration at the steady state, 10-, 33- and 100-fold C_{max}) and a single concentration for the model inducers were tested.	
Results: Induction of CYP1A2, 2B6 and 3A4/5 activities was observed when human hepatocytes were exposed to appropriate positive control inducers. This demonstrated the viability of the hepatocytes. There was no induction of above CYP activities when hepatocytes were exposed to 3, 30 and 100 ug/mL of droxidopa. At 300 ug/mL concentration droxidopa seemed to be cytotoxic to hepatocytes.	
Comments: Droxidopa has low potential for metabolic drug-drug interactions based on CYP induction.	

Reference ID: 3101864

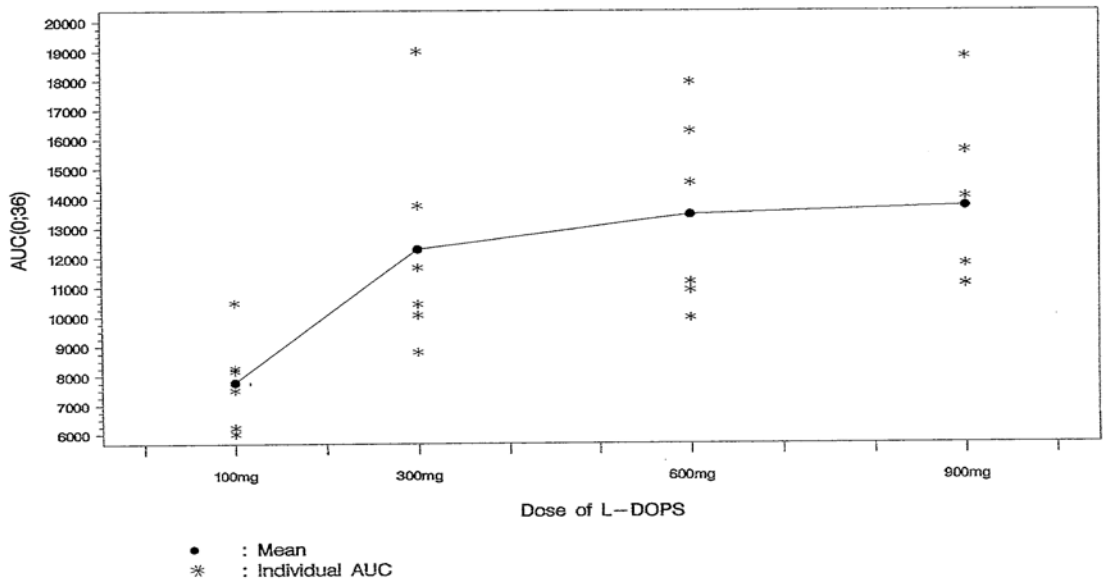
1.3 PHARMACOKINETIC STUDIES

1.3.1 Single Ascending Dose PK studies

Study No. 20/1859-94	**Single Rising Dosage (100, 300, 600, and 900 mg) and Tolerability Study of L-DOPS in Young, Healthy, Male Caucasian Volunteers**
EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\20-1859-94	
Objective: To determine the pharmacokinetics and tolerability of droxidopa	
Study Design: Single-center, double-blind, placebo-controlled phase 1 study in 32 young, healthy, male Caucasian subjects. • Four treatment groups, with 6 subjects on droxidopa and 2 subjects on matching placebo • 100, 300, 600 and 900 mg single oral doses of droxidopa • Dose administration after overnight fasting. PK Blood Samples: Pre-dose, 30, 60, 90, 120, 180 min, 4, 5, 6, 8, 12, 24, 36 h post dose	
Results: Geometric mean concentrations of droxidopa (ug/mL) and 3-OM-DOPS (ng/mL) are shown below:  	



The $AUC_{0\text{-}36h}$ (ng.h/L) of norepinephrine with different dose of droxidopa (mg) are shown below.



Comments:

- Single dose of droxidopa (up to 900 mg) were found to be safe and well tolerated. Blood pressure and pulse rate were also monitored during safety evaluation in all subjects and there was no significant dose-BP relationship for droxidopa.
- Droxidopa was rapidly absorbed and exhibited a median elimination half life of 1.3 to 2 hours across the dose range studied.
- The PK of droxidopa was linear up to 600 mg dose. There was no apparent

difference in exposure to droxidopa and 3-OM-DOPS between the 600 mg and 900 mg doses.

- All does levels of droxidopa provided norepinephrine levels higher than that observed in placebo group. Exposure to norepinephrine with 300, 600 and 900 mg doses of droxidopa were comparable.

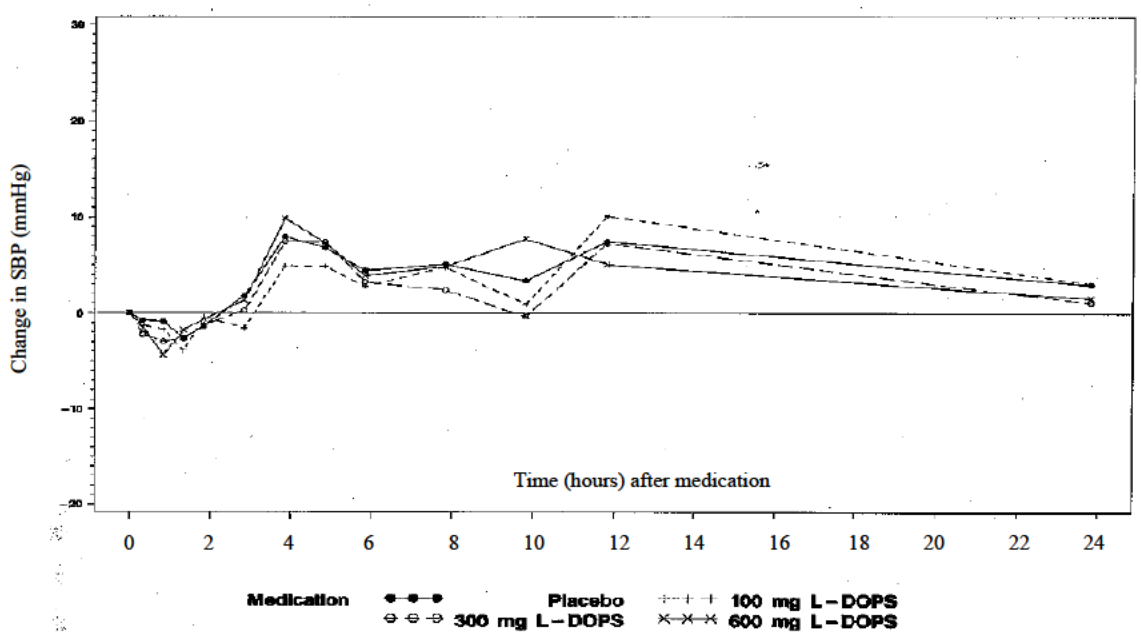
Study No. 20/1860-94	**A single-dose, double-blind, placebo-controlled, 4-period crossover study of L-DOPS (100, 300 and 600 mg) in young healthy, male Caucasian volunteers**

EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\20-1860-94

Objective: To determine the PK of single doses of droxidopa and its metabolite norepinephrine

Study Design: Single-dose, double-blind, placebo-controlled, 4-period cross-over, phase 1 study in 20 healthy, male Caucasian subjects.
Doses studied: 100, 300 and 600 mg
PK Blood Samples: Pre-dose, 30, 60, 90, 120, 180 min, 4, 5, 6, 8, 12, 24 h post dose

Results:
Droxidopa was rapidly absorbed, with maximum plasma concentrations attained in about 2-4 hours post dose. The median elimination half life of droxidopa was about 2 hours. Maximum plasma levels of norepinephrine were observed within 8 hours of dose administration in all subjects. Blood pressure and pulse rate were monitored as part of the safety evaluation in all subjects. Time course of mean change in SBP after subjects have rested in supine position is shown below:



Comments:

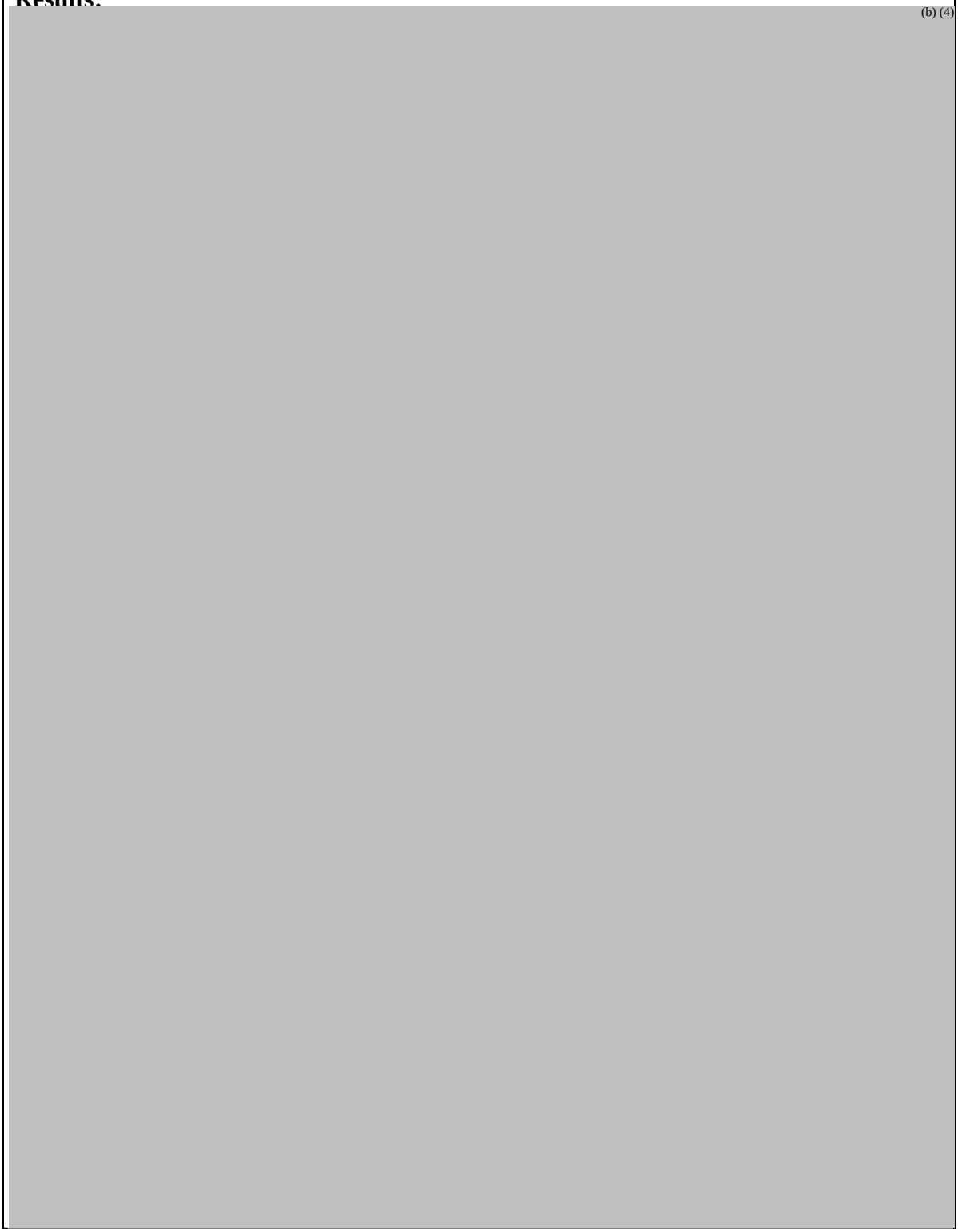
- The PK of droxidopa was linear and almost dose proportional within the 100-600

mg dose range. BP effects observed during safety monitoring were not significantly different across treatment arms. • All does levels of droxidopa provided norepinephrine levels higher than that observed in placebo group. Exposure to norepinephrine with 100, 300 and 600 mg doses of droxidopa were comparable and no dose-adequate changes were observed.

1.3.2 Multiple Dose PK/Pivotal BE/Food Effect Studies

Study No. 101	**Food effect, Pivotal Bioequivalence and Multiple-Dose PK study**
Title	A randomized, open-label, three-period, three sequence, single-dose crossover and separate three-daily-dose treatment period study comparing the PK profiles following oral dosing of 300 mg of droxidopa in the Fed versus Fasted State, the bioequivalence of three 100 mg capsules of droxidopa versus a single 300 mg capsule of droxidopa, and 300 mg of droxidopa given three times at four hour intervals in health, elderly subjects
Study Design	
☑Bioequivalence ☑ Food Effect	
Part I	
Treatment A: 3 x 100 mg capsules, Fasted Treatment B: 3 x 100 mg capsules, Fed Treatment C: 1 x 300 mg capsule, Fasted Treatments A and C were administered after a minimum 10-hour fast. Treatment B was administered 30 minutes after subjects began a standard high calorie, high fat breakfast.	
PK Sampling: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after dosing on treatment days for droxidopa plasma concentrations	
Part II	
Open-label design. Three separate doses of 3 ×100 mg capsules of droxidopa (300 mg total per dose) at 4 h intervals (0800, 1200, and 1600 hours)	
PK Sampling: Blood samples for measurement of the concentration of droxidopa, 3-OM-DOPS, and NE were collected at 0.5, 1, 1.5, 2, 3, 4 (prior to second dose), 4.5, 5, 5.5, 6, 7, 8 (prior to the third dose), 8.5, 9, 9.5, 10, 11, 12, 14, 16, 18, 24 hours (times are relative to the first dose)	
Analytical Method: Plasma concentrations of the analytes were measured using validated methods. OSI has conducted a site inspection for BE clinical and analytical site. The inspection report describes inadequate assay validation and QC procedures and suggests the bioanalysis is not reliable in the BE part of the study.	
Statistical Method: • Part I: ANOVA on log transformed parameters fitting for sequence, period, treatment and subject within treatment. Geometric mean ratios and 90% CI were constructed for 3 x 100mg fed-to-3 x 100 mg fasted and 1 x 300 mg fasted-to-3 x 100 mg fasted Part II: Descriptive statistics and graphical displays on PK parameters for multiple doses (three doses at 4h intervals) as well as the comparisons of multiple doses to the single dose.	

Reference ID: 3101864

Study Population : 24 healthy, elderly, male or female subjects
Results: (b) (4) 

(b) (4)

Site Inspected	
Requested: Yes	**Performed:** Yes
Safety	

▪ Was there any death or serious adverse events? ☑ No
Conclusion
(b) (4)
Comments
(b) (4) • Final OSI report after the clinical/bioanalytical site inspection described reliability issues with the bioanalysis during the BE study and recommended non-approval of the pivotal BE study (Ref. Memorandum to file by Dr. Jangik I Lee, DARRTS date 24-January 2012). Therefore, the BE results from this study is not acceptable and the new 300 mg capsule formulation cannot be approved based on the above BE study.

1.4 PHASE II STUDIES

Study No. 50/2034–94	**Efficacy and safety of three different dosages (200 mg, 400 mg and 600 mg) of L-threo-DOPS compared with placebo in patients with familial amyloid polyneuropathy (FAP)**
EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\noh-symptoms\5351-stud-rep-contr\50-2034-94	
Objective: To compare the efficacy and safety profiles of three incremental dosing regimens with those experienced after a visually identical placebo. The assessments were the quantification of standing time on a tilt table and the concomitant assessment of orthostatic symptoms.	
Study Design: Randomized, multi-center, double-blind, placebo-controlled, cross-over, phase II study. **Dose Groups:** Placebo, 200, 400 and 600 mg per day in BID regimen **Primary Endpoint:** Standing time on tilt table at 60 degrees and orthostatic hypotension symptom rating scale A total of 37 patients with FAP were randomized. The structure of the 14 week study	

period is shown below:

Period	Duration	Dosage for patients in Group I	Dosage for patients in Group II
Run-in	1 week	Placebo	Placebo
Period 1	6 weeks	L-threo-DOPS: 2 weeks 100 mg bid then 2 weeks 200 mg bid then 2 weeks 300 mg bid	Placebo
Wash-out	1 week	Placebo	Placebo
Period 2	6 weeks	Placebo	L-threo-DOPS: 2 weeks 100 mg bid then 2 weeks 200 mg bid then 2 weeks 300 mg bid

Results:

The primary efficacy endpoint, orthostatic symptom rating scale, is shown below:

Comparison	Day	Estimated difference	95% CI lower bound	95% CI upper bound	*p* value Wilcoxon
200 mg L-threo-DOPS – Placebo	14	–0.05	–1.12	1.01	0.8165
400 mg L-threo-DOPS – Placebo	28	0.09	–0.73	0.91	0.9756
600 mg L-threo-DOPS – Placebo	42	–0.02	–0.77	0.72	0.9027

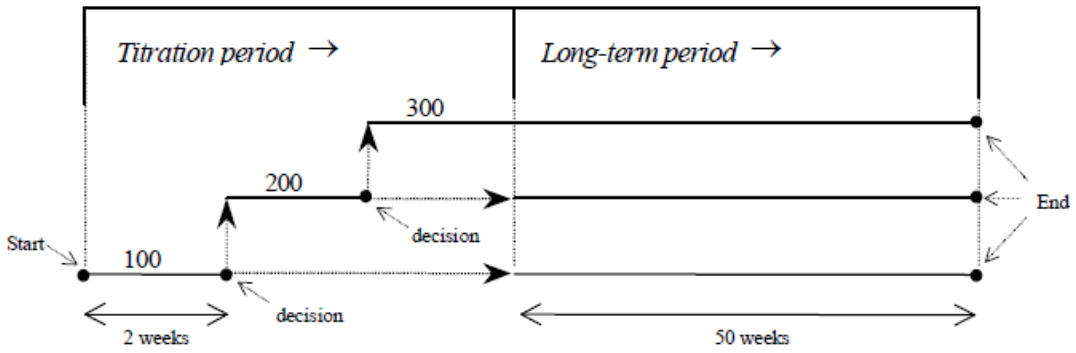
The average change between baseline and day 42 in mean BP for droxidopa treated patients were numerically larger (~7.0 ±7.0 mmHg) than that in placebo treated patients (~0.3 ± 7.3 mmHg).

The standing time (mm:ss) on the tilt table at 60 degrees is shown below:

Comparison	Day	Estimated difference	95% CI lower bound	95% CI upper bound	*p* value Wilcoxon
200 mg L-threo-DOPS – Placebo	14	0:16	–1:06	1:38	0.9079
400 mg L-threo-DOPS – Placebo	28	–0:06	–1:16	1:03	0.8452
600 mg L-threo-DOPS – Placebo	42	–1:28	–2:55	–0:01	0.3719

Comments:

- Droxidopa administered as 100, 200 and 300 mg BID were well tolerated.
- The study failed to show a clear reduction in orthostatic symptoms including standing time on a tilt table and orthostatic drop in BP.

Study No. 2175	**Efficacy and safety of three different dosages (200 mg, 400 mg and 600 mg) of L-threo-DOPS compared with placebo in patients with familial amyloid polyneuropathy in an open follow-up study** ***Note: This is an open label long term extension to Study No. 50/2034–94***
EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\noh-symptoms\5352-stud-rep-uncontr\2175	
Objective: To evaluate the safety profile of long-term treatment with L-threo-DOPS.	
Study Design: European multi-national, randomized, open, uncontrolled, dose-titration study as a follow-up phase. Two to six weeks dose-titration phase with visit intervals of two weeks. Thereafter, long-term treatment for 50 weeks with visit intervals of eight weeks, except the last interval of 10 weeks. Overall duration of follow-up was thus planned to vary between 52 and 56 weeks. Schematics of the study design is shown below:  **Dose Groups:** Placebo, 200, 400 and 600 mg per day (total daily dose) in BID regimen. Dose increases during titration was optional based on the patients orthostatic symptoms.	
Results: Scores for the three symptoms: dizziness, fainting and blurred vision, ranging from 0 (absent) to 4 (very frequently present), were summed for each patient at each visit of the follow up study. This gave each patient a sum-score between 0 and 12 as shown below:	

Reference ID: 3101864

	Absolute sumscore			Changes from baseline		
	n	Mean ± SD	Range	n	Mean ± SD	Range
Baseline	33	6.73 ± 2.34	3 – 12	–	–	–
Visit 11	33	2.64 ± 1.27	1 – 7	33	–4.09 ± 1.99	-9 – 0
Visit 12	4	2.50 ± 0.58	2 – 3	4	–6.00 ± 2.31	-8 – -4
Visit 14	32	2.59 ± 1.13	1 – 7	32	–4.03 ± 1.94	-9 – 0
Visit 15	30	2.50 ± 0.90	1 – 5	30	–4.00 ± 2.15	-10 – -1
Visit 16	27	2.48 ± 1.25	1 – 5	27	–3.74 ± 1.72	-8 – -1
Visit 17	27	2.56 ± 1.12	1 – 5	27	–3.67 ± 1.88	-8 – -1
Visit 18	27	2.37 ± 1.15	0 – 5	27	–3.85 ± 1.75	-8 – -2
Visit 19	27	2.63 ± 1.15	1 – 5	27	–3.59 ± 1.93	-8 – -1
Last visit	33	2.70 ± 1.10	1 – 10	33	–4.03 ± 2.27	-10 – -1

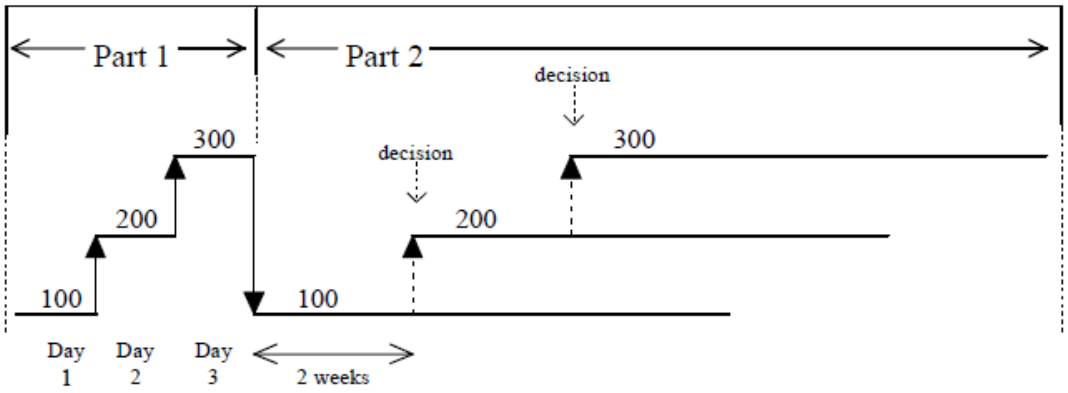
The visits 11 & 12 correspond to dose titration phase. Visits 14 - 19 correspond to visits during the long term phase.
The mean standing time on the tilt table at 60 degrees increased from 2 min 34 seconds at baseline to 8 min 44 seconds at visit 19. However, after visit 11 only a slight further improvement was seen during the follow up part of the study (See below).

	Absolute standing time			Changes from baseline and confidence interval for mean (lower and upper limit)			
	n	Mean ± SD	Range	n	Mean ± SD	Range	95% CI for mean
Baseline	33	2:34 ± 2:00	0:23 – 10:00	–	–	–	–
Visit 11	33	8:01 ± 2:27	2:17 – 10:00	33	5:27 ± 2:34	0:00 – 9:32	4:32; 6:21
Visit 12	4	6:27 ± 1:34	4:28 – 8:06	4	5:30 ± 1:54	2:48 – 7:11	2:52; 8:09
Visit 14	32	8:22 ± 2:20	1:30 – 10:00	32	5:45 ± 2:23	0:00 – 9:27	4:53; 6:36
Visit 15	30	8:46 ± 1:54	4:38 – 10:00	30	6:03 ± 2:03	0:00 – 9:37	5:17; 6:48
Visit 16	27	8:45 ± 1:48	5:08 – 10:00	27	5:55 ± 1:58	0:00 – 9:37	5:08; 6:42
Visit 17	27	8:53 ± 1:44	5:04 – 10:00	27	6:02 ± 2:07	0:00 – 9:37	5:12; 6:52
Visit 18	27	8:21 ± 1:54	4:20 – 10:00	27	5:30 ± 1:52	0:00 – 8:40	4:46; 6:15
Visit 19	27	8:44 ± 1:49	4:02 – 10:00	27	5:54 ± 2:00	0:00 – 8:58	5:06; 6:41
Last visit	33	8:39 ± 1:50	4:02 – 10:00	33	6:05 ± 2:03	0:00 – 9:27	5:21; 6:48

Comments:

- Droxidopa was well tolerated by FAP patients during the follow up phase of the study.
- Symptoms such as dizziness, blurred vision and fainting were slightly reduced during the first weeks of treatment and improvement was maintained during long term open label treatment. Similar pattern was seen for the standing time on tilt table as well. However this is an open label extension study with no placebo control.

Reference ID: 3101864

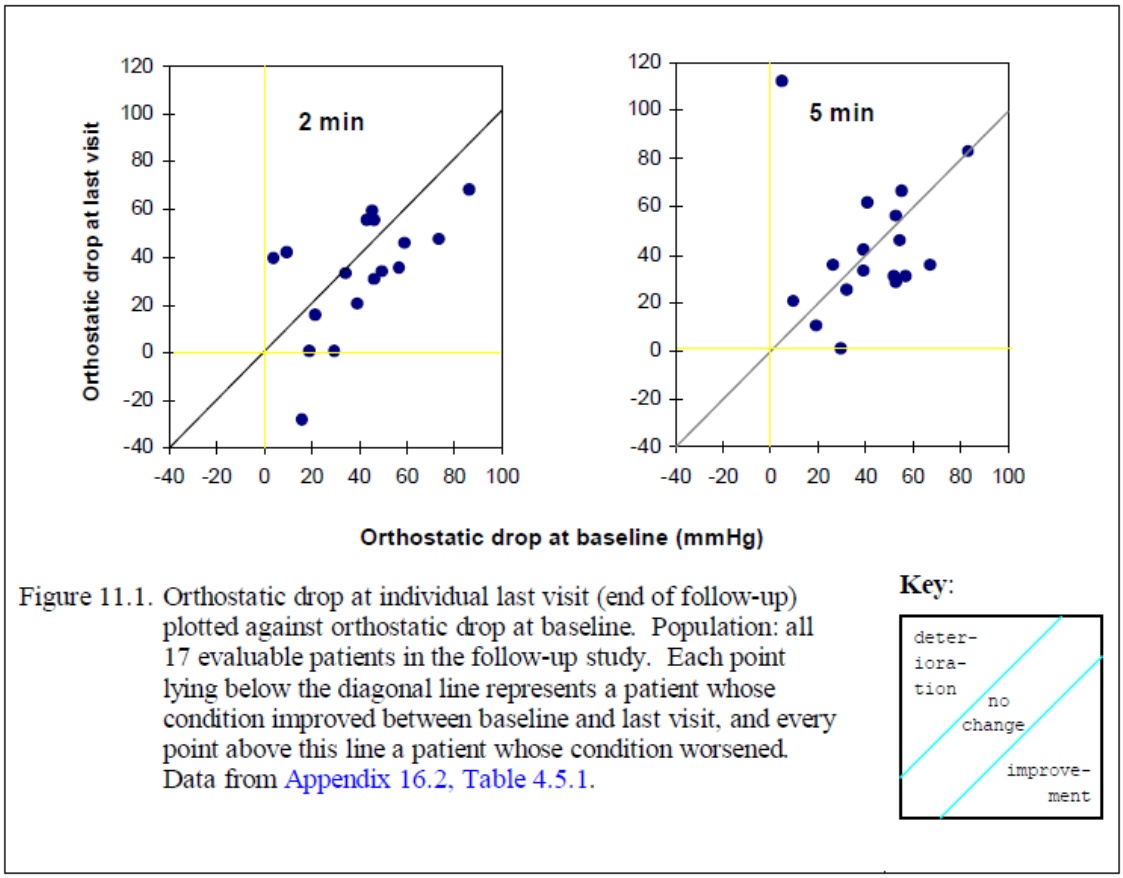
Study No. 50/2062-94	**A dose-titration study of three different dosages (200 mg, 400 mg and 600 mg) of L-threo-DOPS on orthostatic hypotension in patients with pure autonomic failure or shy–drager syndrome/multi-system atrophy**
EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\noh-symptoms\5352-stud-rep-uncontr\50-2062-94	
Objective: To determine the individual optimal dosage of L-threo-DOPS (100, 200 or 300 mg bid) in the treatment of postural hypotension symptoms of pure autonomic failure (PAF) or Shy–Drager syndrome/multiple system atrophy (SDS/MSA) and to assess the safety and tolerability of these three dosages of L-threo-DOPS.	
Study Design: Phase 2, European multi-national, multi-centre, open, uncontrolled dose-titration study. A total of 32 patients were enrolled in the study. Doses: 100, 200 and 300 mg BID. Part 1 includes a 3 day dose titration with clinical symptom assessment and part 2 (out patient phase) with a dose titration and maintenance as shown below:  	
Results: The primary efficacy variable was orthostatic drop in BP measured at 2 and 5 minutes after standing up. Initial mean fall in BP at 2 and 5 minutes were approximately 51 and 52 mmHg respectively. During the final study visit the mean fall in BP was about 32 mmHg after 5 minutes standing. Clinical symptom assessment during study visits is shown below:	

Reference ID: 3101864

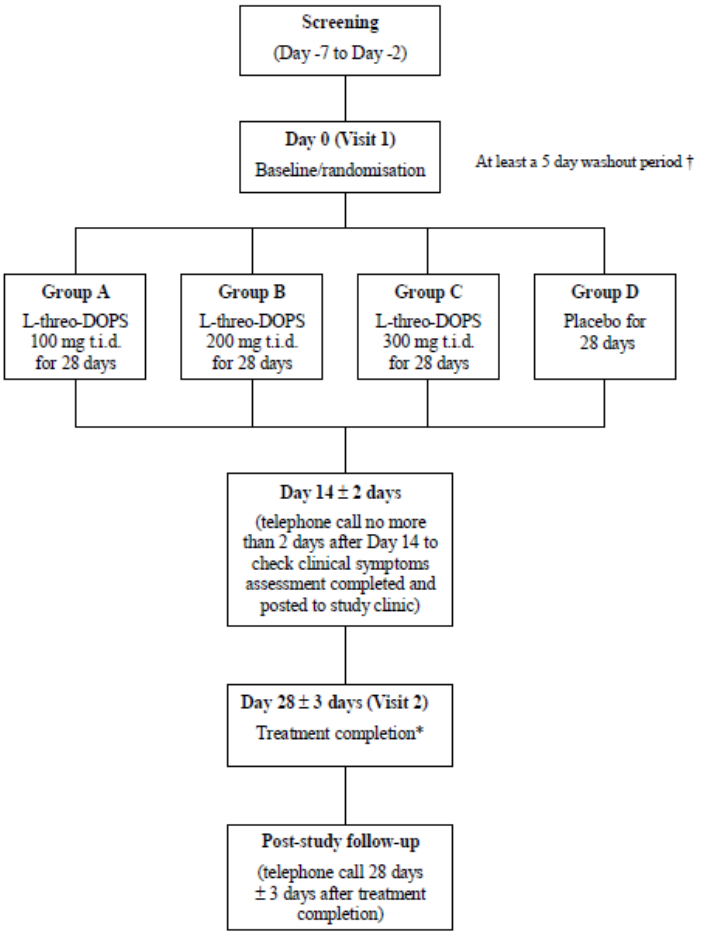
Symptom	Difference from baseline at	Mean change from baseline	p-value
Light-headedness/dizziness	Last visit	–1.28	0.0125
(baseline score 4.72)	Visit 2 (post-dose)	–1.31	0.1892
	Visit 4	–1.53	0.0433
	Visit 8	–1.71	0.0075
Weakness/fatigue/tiredness	Last visit	–0.41	0.5572
(baseline score 5.93)	Visit 2 (post-dose)	–1.16	0.0309
	Visit 4	–0.77	0.5235
	Visit 8	–1.05	0.1435
Standing	Last visit	0.41	0.4244
(baseline score 5.22)	Visit 2 (post-dose)	–0.16	1.0000
	Visit 4	0.17	0.2632
	Visit 8	0.24	0.4545
Walking	Last visit	0.00	0.6476
(baseline score 6.13)	Visit 2 (post-dose)	–0.06	1.0000
	Visit 4	0.13	0.8036
	Visit 8	0.10	1.0000
Usual activities	Last visit	–0.59	0.4049
(baseline score 7.34)	Visit 2 (post-dose)	–0.09	0.4545
	Visit 4	–0.50	0.5034
	Visit 8	–0.57	0.8145
Blurred vision	Last visit	–1.00	0.0290
(baseline score 3.94)	Visit 2 (post-dose)	–1.38	0.0007
	Visit 4	–1.73	0.0026
	Visit 8	–0.67	0.0574

(Visits 2, 4 and 8 corresponds to day 1, day 3 and week 8, respectively)

Comments:
Droxidopa was well tolerated and the study showed evidence of symptom relief as measured in the clinical symptom assessment and decreased orthostatic fall in BP after 5 minutes standing compared to baseline. Dose titrations in part 1 and 2 of the study provided comparable results suggesting that daily dose-titration with monitoring may be beneficial in reaching the target dose faster.

Study No. 2210	**A dose-titration follow-up study of three different dosages (200 mg, 400 mg and 600 mg) of L-threo-DOPS on orthostatic hypotension in patients with pure autonomic failure or shy–drager syndrome/multi-system atrophy** ***Note: This is an extension study to Study No. 50/2062-94***
EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\noh-symptoms\5352-stud-rep-uncontr\2210	
Objective: The primary objective of this follow-up study was to evaluate the safety profile of long-term treatment with L-threo-DOPS. Efficacy was assessed as a secondary objective.	
Study Design: European multi-national, multi-centre, open, uncontrolled dose-titration study. This is a follow up study to **50/2062-94.** Patients were initially given the same doses that they had received at the end of the initial study. Thereafter, doses could be raised or lowered in 100-mg steps, at the discretion of the investigator, between 100 and 300 mg BID. Data from 17 patients were available for efficacy evaluation.	
Results: There was no primary efficacy variable as such in the follow-up part of the trial. Relevant variables for efficacy in follow-up were haemodynamic parameters and the Clinical Symptoms Checklist. Orthostatic drop in BP up on standing are shown below:  Figure 11.1. Orthostatic drop at individual last visit (end of follow-up) plotted against orthostatic drop at baseline. Population: all 17 evaluable patients in the follow-up study. Each point lying below the diagonal line represents a patient whose condition improved between baseline and last visit, and every point above this line a patient whose condition worsened. Data from Appendix 16.2, Table 4.5.1. **Key**: 	
Comments: • Droxidopa was well tolerated during the follow up part of the trial. • There was a slight trend towards reduction in orthostatic drop up on standing.	

Reference ID: 3101864

Study No. S10002	**A phase II, multi-centre, multi-national, randomized, placebo-controlled, parallel group, double-blind study to investigate the optimal dose of L-threo-DOPS in the treatment of orthostatic hypotension in patients with multiple system atrophy or Parkinson's disease**
EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\noh-symptoms\5351-stud-rep-contr\s10002	
Objective: The primary objective of the study was to determine the optimal dose [the minimum effective dose (MED) that shows a reduction in the fall in orthostatic systolic blood pressure (SBP) compared with placebo and has an acceptable safety profile] of L-threo-DOPS for preventing the fall in SBP in orthostatic hypotension in patients with multiple system atrophy (MSA) or Parkinson's disease.	
Study Design: Phase II, multi-centre, multi-national, randomized, placebo-controlled, parallel group, double-blind, double-dummy study with 4 treatment arms. The study consisted of a screening period (2-7 days) and a 28-day treatment period. There were three visits: screening, Day 0 and Day 28; a clinical symptoms assessment was to be completed by patients on Day 14 and there was to be a follow-up safety telephone call 28 days ± 3 days after the completion of study treatment (See below).  Patients were to be randomized to receive L-threo-DOPS 100, 200 or 300 mg TID or	

placebo. A total of 125 patients were enrolled in to the study.

Results: The primary efficacy endpoint was the reduction in fall in SBP measured after 10 minutes in the supine position and 6 minutes in the head up tilt position between day 0 pre-dose and day 28, as shown below (ITT population):

	Reduction in fall in SBP $\Delta F_{S\ Day\ 28}$ (mmHg)			
	100 mg t.i.d. n=33	**200 mg t.i.d. n=27**	**300 mg t.i.d. n=31**	**Placebo n=30**
Mean (SD)	3.5 (24.05)	2.5 (15.09)	4.9 (25.15)	-6.7 (22.68)
Median	2.0	6.0	5.5	-4.0
Range (min-max)	-40 - 71	-31 - 21	-39 - 77	-62 - 39
p-value	-	-	0.035	-

Comments:

- Droxidopa exhibited a tolerable safety profile in the patient population.
- 300 mg TID appears to be the minimum effective dose among the doses studied here in reducing orthostatic fall in BP

Study No. S10002a	**<u>Additional open-label extension</u> to a phase II, multicentre, multi-national, randomized, placebo-controlled, parallel group, double-blind study to investigate the optimal dose of L-threo-DOPS in the treatment of orthostatic hypotension in patients with multiple system atrophy or Parkinson's disease**

EDR: \\cdsesub1\EVSPROD\NDA203202\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\noh-symptoms\5352-stud-rep-uncontr\s10002a

Objective: To obtain long-term safety and tolerability data on L-threo-DOPS in patients who completed Visit 2 of the S10002 study.

Study Design: Phase II, open-label extension to the S10002 study. 78 patients were available for safety evaluation. Planned duration of treatment was at least 12 months.

Comments:

- Droxidopa was generally well tolerated in this patient population. Nine patients died, but the deaths were not considered to be associated with droxidopa.
- Most treatment-emergent AEs occurred in the titration phase (headache, dizziness, somnolence and hypertension). There appeared to be no relationship between dosages and the intensity, onset, duration or frequency of AEs.

2. POPULATION PK ANALYSIS

The purpose of this review is to address the following key question.

Are the labeling recommendations based on the population pharmacokinetic analysis of droxidopa and its metabolite (3-OM-DOPS) acceptable?
Yes, the labeling recommendations are acceptable with minor changes (see below for details).

Age and co-administration of L-DOPA with dopa-decarboxylase inhibitors significantly affected exposure to droxidopa and 3-OM-DOPS, as demonstrated in Figure 1. Age explained ~4% of inter-individual variability on droxidopa clearance while co-administration of L-DOPA explained ~14% of the variability.

Reviewer's analyses indicated that droxidopa clearance decreases with age, with about 0.8% per year after age of 65 years; co-administration of L-DOPA decreases the median of droxidopa clearance by 53% (Table 1) and 3-OM-DOPS clearance by ~27% , respectively, which is consistent with values reported by the sponsor. Other covariates, such as sex, body weight, ALT, AST, and CRCL does not influence the PK of droxidopa and 3-OM-DOPS. Race effect can not be estimated here because too few subjects were available for each group as most subjects were white.

Table 1: Reviewer's final PK model parameter estimates for droxidopa

Fixed Effects Parameters	Estimate	Inter-individual variability (%)
CL/F (Clearance, L/day)	702	41.4
V_1 (Central Volume, L)	40.8	29.8
CLdistribution/F (L/day)	130	106.3
V_2/F (Peripheral Volume)	178.0	30.1
RXFactor-No L-DOPA	1	-
RXFactor-With L-DOPA	0.528	-
AgeFactor on CL	0.00791	-
Mean absorption time (days)	0.241	-
Shape factor for mean absorption time	0.658	62.0

Reference ID: 3101864

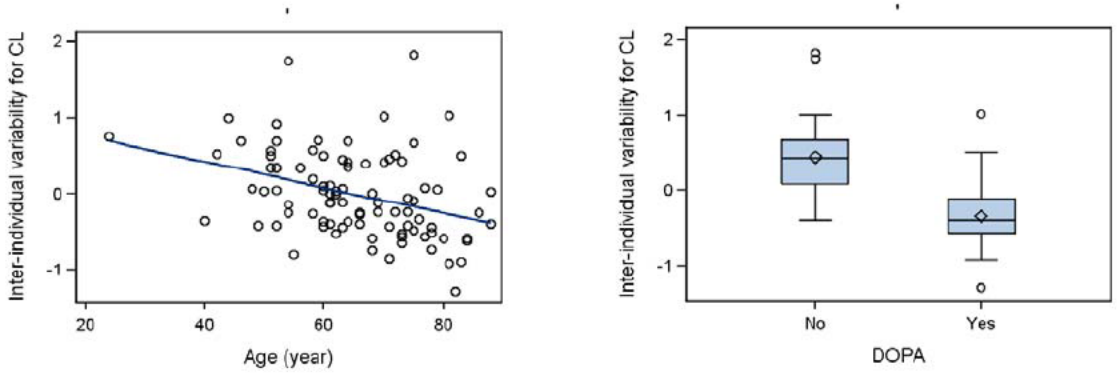


Figure 1: Graphical analysis of inter-individual variability vs. covariates for droxidopa

Recommendations

The Division of Pharmacometrics has reviewed the submission (NDA 203202) and found it acceptable, provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the labeling text.

Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

Pertinent Regulatory Background

Results of Sponsor's Analysis

The sponsor conducted pharmacokinetic analyses using data collected from Study 302. Population PK models were developed to characterize the pharmacokinetic profile of droxidopa and its major metabolite, 3-OM-DOPS. Plasma concentration data for droxidopa, 3-OM-DOPS were determined using an LC-MS/MS assay and were

Reference ID: 3101864

assembled into NONMEM datasets, along with other data such as dosing history, laboratory, and demographics.

A total of 91 subjects were included in the dataset for droxidopa, of which, 61.54% are male, and 38.46% female; 96.7% are white and 1.1% for Asian, American Indian and Hispanic, respectively, with median age of 64 years (range: 24-88 years) and mean weight of 74 kg (range: 38.6-102 kg).

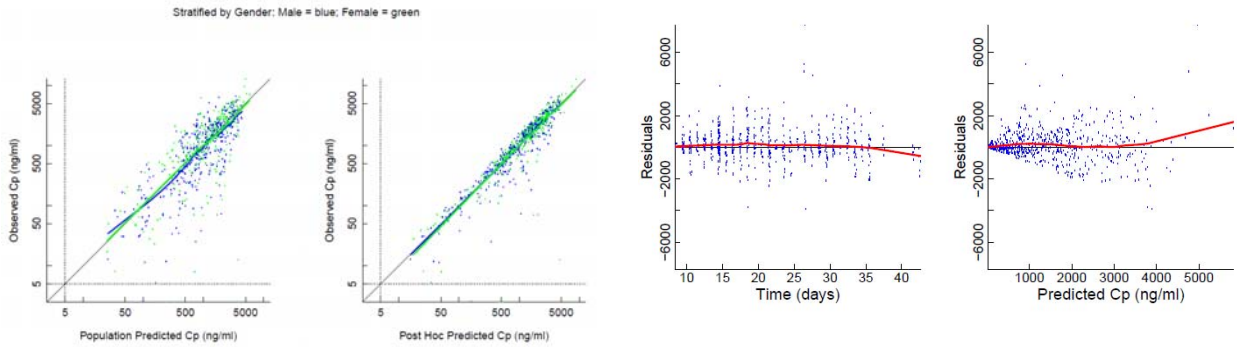
For droxidopa, a two-compartment model with inverse Gaussian absorption and first-order elimination was adequate to describe the data. For 3-OM-DOPS, a one-compartment with first-order forming process and first-order elimination was found fitting the data well. Post hoc parameter estimates from optimal model for droxidopa and 3-OM-DOPS are summarized in Table 2 and Table 3, respectively. The goodness-of-fit plots for the droxidopa are presented in Figure 2.

Table 2: *Post hoc* estimated parameters for the optimal model for droxidopa

Description	Mean	Standard Deviation	Median	Minimum	Maximum
CL / F (L / day)*	535.4	379.8	426.7	110.1	2459
V_1 / F (L)*	41.8	10.9	40.3	22	71.6
$CL_{distribution}$ / F (L / day)*	223.3	435.1	121.2	10.5	3024
V_2 / F (L)*	172.3	51.4	164.7	76.8	376.1
Mean absorption time (days)	0.1931	0.0373965	0.19464	0.094408	0.27392
Shape factor for mean absorption time	0.76255	0.45024	0.65689	0.2124	2.266

* In the absence of an intravenous dose of droxidopa, all systemic parameters are normalized by an unknown bioavailability factor (F).

Source: Table 4 on page 6 of sponsor's population PK report



Source: set 51a on page 523, set 71c on page 555 of sponsor's report; similar results were observed for 3-OM-DOPS but are not shown here.

Figure 2: Goodness-of-fit plots for the final model for droxidopa

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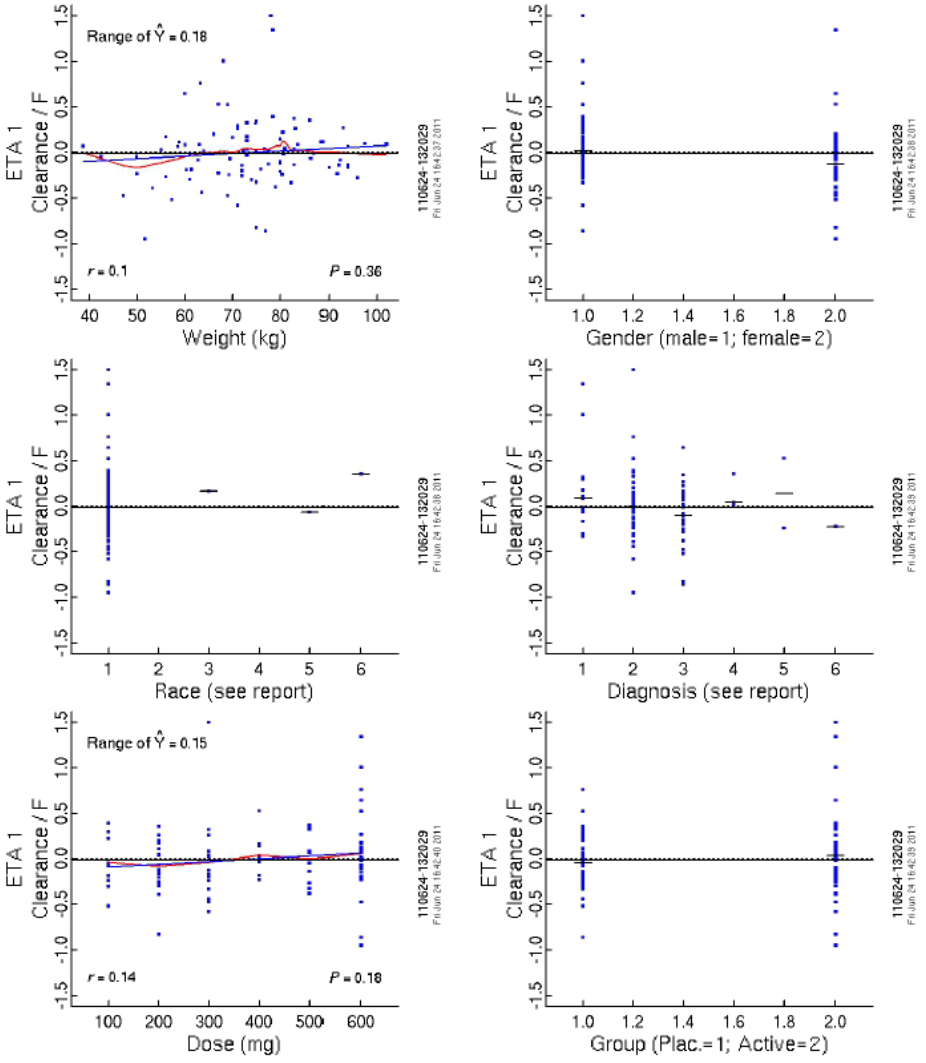
Table 3: *Post hoc* estimates parameters for the optimal model for 3-OM-DOPS

Description	Mean	Standard Deviation	Median	Minimum	Maximum
CL / Fm (L / day)*	64.3	37.6	52.5	19.7	194
V_1 / Fm (L)*	48.8	18.4	44.6	14.6	124.9

*Both systemic parameters are normalized by a composite factor, Fm, that is a function of bioavailability of droxidopa and fraction of droxidopa converted to 3-OM-DOPS.

The sponsor assessed the effect of covariates on PK properties of droxidopa and 3-OM-DOPS. Relationship between investigated covariates (dose, age, gender, race, weight, height, BMI, country, hepatic function [ALT, AST, alkaline phosphatase, total bilirubin], renal function [creatinine clearance], concomitant medications) and post hoc etas were studied, with no noticeable relationship (Figure 3).



Source: Figure 16 on page 48 of sponsor's population PK report

Figure 3: Plots of *post hoc* Eta values vs. Covariates for droxidopa.

Reference ID: 3101864

Reviewer's Comments: The population PK analyses conducted by the sponsor appears reasonable and are acceptable. Noticeably, age and co-administration of L-DOPA are two identified covariates that affect droxidopa and 3-OM-DOPS pharmacokinetic Inclusion of age in the structure model explained about ~4% of inter-individual variability for droxidopa clearance while co-administration of L-DOPA explained ~14 % of the variability.

Droxidopa clearance decreases with age. After age 65, clearance decrease 0.8% per year; co-administration of L-DOPA (including dopa-decarboxylase inhibitor) decreases the median of droxidopa clearance by 53% and 3-OM-DOPS clearance by ~27%, respectively. Consequently, L-DOPA results in about a two-fold increase in drug exposure (AUC) and a 50% increase in exposure to 3-OM-DOPS.

While age and co-administration of L-DOPA derivatives causes significant increase in exposure of droxidopa and metabolites, they do not affect droxidopa effectiveness and safety profile, therefore are not warrant for dose adjustment.

Methods, Datasets and Results from Reviewer's Analysis

The population PK analyses were conducted with NONMEM 7.2 on a high performance Sun Grid Engine Cluster (48-CPU, Redhat Enterprise Linux 5.7). Datasets used are summarized in Table . SAS 9.2 for Windows and NONMEM 7.2 for Linux 64 bit were used in the reviewer's analyses

Table 4. Analysis data sets, analyses codes and output files

Study Number	**Name**	**Link to EDR**
STUDY302	chelsea302-2011-06-23.csv	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Droxidopa_NDA203202_FL\Sponsor Data and Reports\Pop_PK Datasets\STUDY302\PARENT
STUDY302	chelsea302-metabolite-110624-132029-2011-07-11.csv	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Droxidopa_NDA203202_FL\Sponsor Data and Reports\Pop_PK Datasets\STUDY302\METABOLITE
File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
run1 mod	Basic Model	\\cdsnas\PHARMACOMETRICS \Reviews\Ongoing PM Reviews\Droxidopa_NDA203202_FL\PPK Analyses\Structure Model
run2429 mod	Final model (Droxidopa)	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Droxidopa_NDA203202_FL\PPK Analyses\Final Model
droxidopa.sas	Eta and PK-Covariate plots-final model	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Droxidopa_NDA203202_FL\PPK Analyses
Droxidopa_basemodel.sas	Eta and PK-covaraite plots-base model	\\cdsnas\PHARMACOMETRICS \Reviews\Ongoing PM Reviews\Droxidopa_NDA203202_FL\PPK Analyses\Structure Model

Reference ID: 3101864

3. PHARMACOGENOMICS REVIEW

NDA/BLA Number	203,202
Submission Date	09/28/2011
Applicant Name	Chelsea Therapeutics
Generic Name	Droxidopa
Proposed Indication	Treatment of Symptomatic Orthostatic Hypotension
Primary Reviewer	Hobart Rogers Pharm.D., Ph.D
Secondary Reviewer	Michael Pacanowski Pharm.D., M.P.H

3.1 Background

Droxidopa is a new molecular entity submitted on 09/28/2011 for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure. Droxidopa is metabolized in part by catechol-O-methyltransferase (COMT), which has clinically relevant genetic variations. The purpose of this review is to identify any significant role that genetic variation could play on either the safety or efficacy of droxidopa and consequently the need for additional pharmacogenomic investigations post-action.

3.2 Submission Contents Related to Genomics

The effects of genetic polymorphisms were not directly studied in any phase of clinical development, and DNA was not collected in phase 3 trials. Thus, analysis of genetic variation cannot be conducted using existing data.

3.3 Key Question and Summary of Findings

3.3.1 Are pharmacogenomic studies indicated on the basis of the PK, safety, and efficacy profile of droxidopa, particularly for COMT?

Droxidopa is an orally administered prodrug, with the major active metabolite being norepinephrine (NE). Droxidopa is converted to norepinephrine by dopa decarboxylase (DDC) which has several amino-acid changing polymorphisms of unknown functional significance (e.g., Arg462Gln, Met217Val) that might decrease droxidopa activation. Droxidopa is also converted into a number of other metabolites (Figure 1) by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). Theoretically, low COMT activity resulting from common, functional genetic variations (i.e., Val158Met) or use of COMT inhibitors might increase NE concentrations, resulting in hypertensive episodes.

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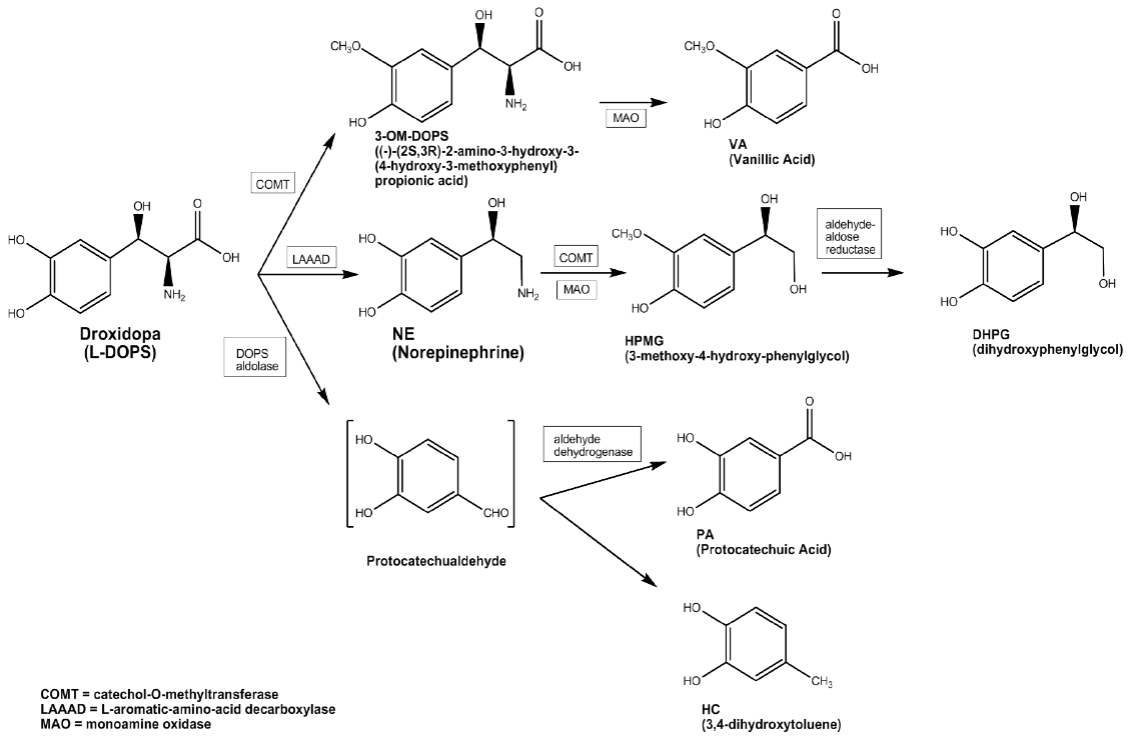

Figure 1. Proposed metabolic pathway for droxidopa. Source: Section 2.7.2, Figure 2-1, Page 10

In pharmacokinetic studies, droxidopa exposures were not highly variable with CV% of approximately 30-35% for both AUC and Cmax. Bi/trimodal distributions of PK parameters or outlying concentrations were not readily apparent to suggest an underlying metabolic defect. Insufficient information was available with regard to race effects on PK given the low enrollment of non-white subjects. Therefore, based on the available data, a genetic contribution to variability in the PK of the parent compound is not evident.

The efficacy and safety of droxidopa was evaluated in six Phase 3 trials (301-306). Trials 304 and 306 are ongoing extension studies. In trial 301 (induction design), droxidopa showed a significant difference compared to placebo in the primary endpoint of mean change in composite orthostatic hypotension questionnaire (OHQ) score (0.9 units, P=0.003) and the individual components (e.g., dizziness, vision; secondary endpoints). Trial 302 (withdrawal design) failed to meet its primary endpoint for an effect on the dizziness component of OHQ, but demonstrated efficacy in a number of secondary efficacy endpoints including the entire OHQ composite score.

Droxidopa was relatively well tolerated and the rate of common adverse events was similar to placebo. The most common adverse event experienced was headache (13.3%). The overall incidence of SAEs was low (1.7%) and similar to placebo. In study 301 and 302 the incidence of supine hypertension (SBP > 180 mmHg) at the end of study visit was 3.1% and 1.5% for droxidopa- and placebo-treated subjects, respectively.

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To assess the potential impact of genetic lesions in DDC, COMT, and/or MAO, we reviewed adverse event rates and cardiovascular responses according to use of drugs that inhibit these enzymes. In phase 3 clinical trials, subjects taking concomitant DDC inhibitors had an approximate 2-fold increase in droxidopa exposure, but no significant differences in either safety or efficacy (see Clinical Pharmacology review). Thus, it is unlikely that genetic variation in DDC would result in greater than 2-fold increase in exposure to droxidopa or clinically relevant effects. Moreover, subjects in phase 3 clinical trials who were taking droxidopa enzymatic degradation agents (COMT inhibitors and MAO inhibitors) did not exhibit differential overall adverse event rates (Table 1). Furthermore, analysis of the titration phase of both study 301 and 302 found no significant differences in supine SBP between placebo and droxidopa subjects with Parkinson's disease taking either DDC or COMT inhibitors Figure 2.

Table 1. Overall Summary of AEs During the Randomized Controlled Treatment Phase in Placebo-Controlled Studies by Concomitant Medications

	Placebo		Droxidopa	
	n (%)	E	n (%)	E
Dopa Decarboxylase Inhibitor				
Using, n	62		60	
Any AEs	18 (29.0)	37	11 (18.3)	19
SAEs	1 (1.6)	2	0	0
Related AEs[1]	6 (9.7)	6	7 (11.7)	11
Severe AEs	0	0	0	0
Not Using, n	70		71	
Any AEs	13 (18.6)	21	19 (26.8)	44
SAEs	0	0	0	0
Related AEs[1]	8 (11.4)	9	10 (14.1)	29
Severe AEs	2 (2.9)	2	0	0
Droxidopa Enzymatic Degradation Agent				
Using, n	26		35	
Any AEs	9 (34.6)	21	10 (28.6)	16
SAEs	0	0	0	0
Related AEs[1]	1 (3.8)	1	6 (17.1)	10
Severe AEs	0	0	0	0
Not Using, n	106		96	
Any AEs	22 (20.8)	37	20 (20.8)	47
SAEs	1 (0.9)	2	0	0
Related AEs[1]	13 (12.3)	14	11 (11.5)	30
Severe AEs	2 (1.9)	2	0	0

Source: ISS Table 2-11

Reference ID: 3101864

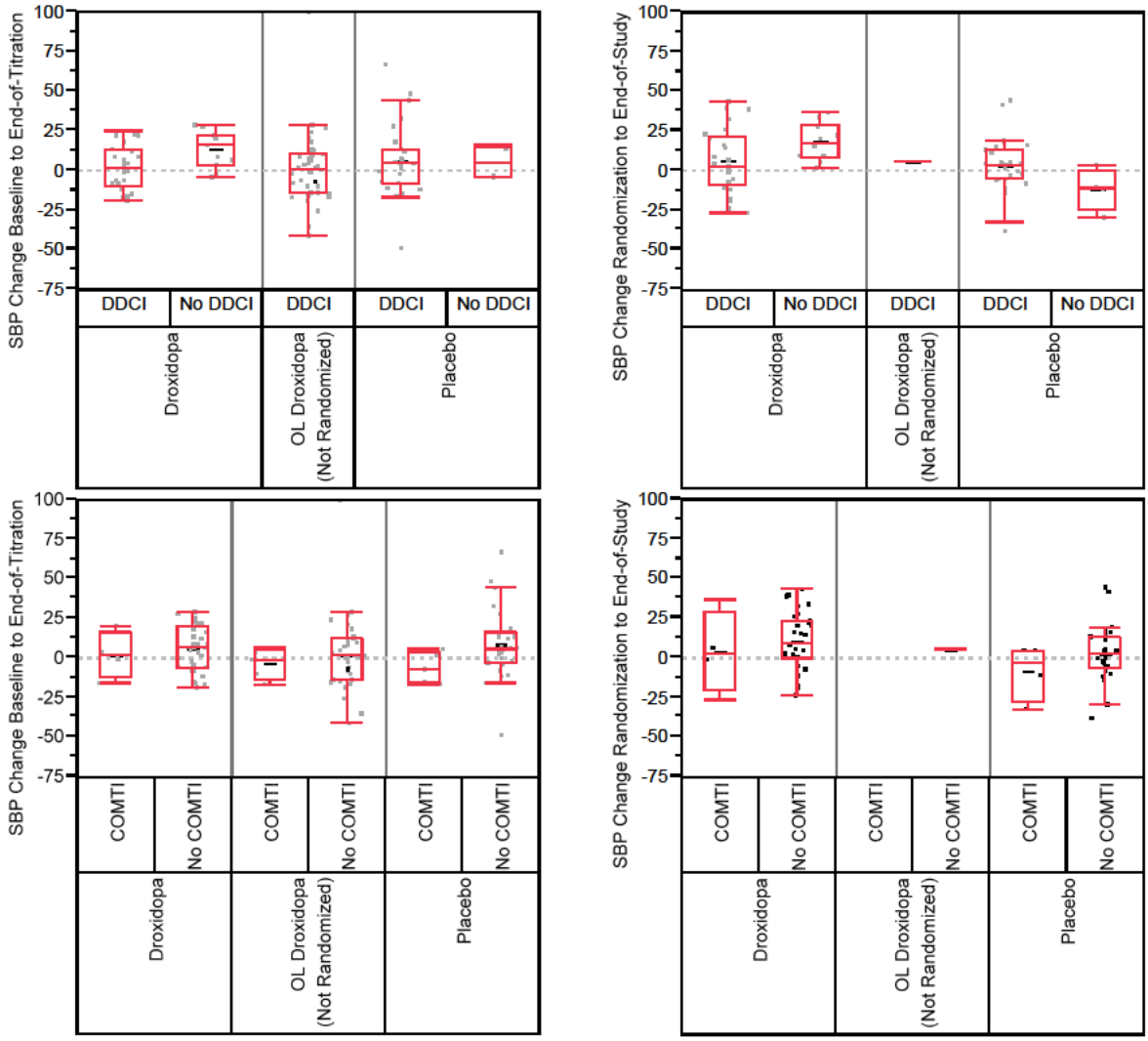

Figure 2. Change in Average Supine Systolic Blood Pressure in Subjects with Parkinson's disease in Open-Label and Randomized Treatment Phases of Study 301 by Use of DDC Inhibitors (top) or COMT Inhibitors (bottom)

The absence of a significant effect of pharmacologic COMT or MAO inhibition may be a function of the fact that the COMT and MOA inhibitors are typically only administered to Parkinson's disease patients who are also receiving DDC inhibitors. In these patients, droxidopa metabolism is likely to be shunted toward the protocatachuic acid pathway rather than NE accumulation.

3.4 Summary and Conclusions

Droxidopa is a prodrug that is converted to its active moiety NE by DDC and to other metabolites by MAO and COMT. Genetic lesions in DDC may result in loss of efficacy (less NE produced) and COMT/MAO may result in adverse events (accumulation of NE).

Significant genetic effects on droxidopa PK are unlikely because droxidopa does not exhibit highly variable PK. Droxidopa appears both safe and effective in the indicated population. Several subjects exhibited large increases blood pressure (in excess of 200 mmHg for systolic BP).

The effect of COMT and MAO gene variants on NE accumulation cannot likely be inferred from the experience with COMT inhibitors because these agents are administered with DDC inhibitors (thus, limited NE is likely to be produced from the parent molecule). Coadministration of either COMT or MAO inhibitors with droxidopa did not significantly increase supine systolic blood pressure or adverse events.

Droxidopa is titrated to effect, which may compensate for any influence of intrinsic or extrinsic factors on droxidopa activation.

3.5 Recommendations

Functional genetic variants do exist for both DDC, COMT, and MAO, however they are unlikely to result in clinically significant effects because droxidopa is titrated to effect and did not appear to have major concerning adverse events attributable to concomitant DDC, COMT or MAO inhibitor use. Additional pharmacogenetic studies do no appear to be indicated.

3.5.1 Post-marketing studies

None.

3.5.2 Labeling recommendations

None.

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/s/

SREEDHARAN N SABARINATH
03/14/2012

FANG LI
03/14/2012

HOBART ROGERS
03/15/2012

MICHAEL A PACANOWSKI
03/16/2012

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03/16/2012

RAJANIKANTH MADABUSHI
03/18/2012

CLINICAL PHARMACOLOGY REVIEW

NDA:	203-202
Submission date:	09/23/2011
Submission Type:	Original NDA (NME - Priority Review)
Brand Name:	Northera®
Generic name:	Droxidopa
Dosage Form & Strengths:	Capsules (100, 200 and 300 mg)
Indication:	Treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure, dopamine β-hydroxylase deficiency and non-diabetic autonomic neuropathy.
Applicant:	Chelsea Therapeutics, Inc.
Review Division:	DCP1 & DCRP
Primary Reviewer:	Sreedharan Sabarinath, PhD
Pharmacometrics Team leader:	Pravin Jadhav, PhD
Pharmacometrics Reviewer	Sreedharan Sabarinath, PhD and Fang Li, PhD
Team Leader	Rajanikanth Madabushi, PhD

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1. EXECUTIVE SUMMARY

Chelsea Therapeutics Inc. has submitted an original new drug application (NDA 203-202) for droxidopa capsules for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (such as Parkinson's disease PD, multiple system atrophy MSA and pure autonomic failure PAF), dopamine β-hydroxylase deficiency (DβH) and non-diabetic autonomic neuropathy (NDAN).

Droxidopa is a synthetic amino acid precursor, which releases norepinephrine (NE) through dopa decarboxylase enzyme. Droxidopa also gets metabolized by the COMT pathway and only 3 metabolites besides NE were quantified in humans and animals. It is possible that droxidopa could generate DOPAL, another metabolite/degradant considered toxic to neurons in humans and animals and the pharmacology/toxicology review team has raised concerns over this possibility.

The clinical development program supporting this NDA included one pivotal efficacy trial (301), a supportive phase III study (302), two long-term extension studies (303 and 304) in NOH patients and a PK/food effect/pivotal bioequivalence (BE) study (Study 101). Studies 301 and 302 were multi-center, double-blind, randomized, placebo-controlled, parallel-group Phase III trials in NOH patients by induction and withdrawal designs, respectively. There was a 24-hour ambulatory blood pressure monitoring (ABPM) study (305) from a subset of patients originally enrolled in study 301. There were no dedicated renal or hepatic impairment studies or drug-drug interaction studies in their drug development program. The proposed dosage form strengths of droxidopa for commercial distribution are 100 mg, 200 mg and 300 mg immediate release capsules.

The pivotal efficacy trial (301) showed a statistically significant (p=0.003) treatment difference of 0.9 units in orthostatic hypotension questionnaire OHQ composite score, a 10-point scale, favoring droxidopa compared to placebo (primary efficacy endpoint). The treatment effect on dizziness (item 1 on orthostatic hypotension symptom assessment OHSA questionnaire), one of the primary NOH symptoms was also favoring droxidopa over placebo (p<0.001). However, the supportive study 302, which used the item 1 of the OHSA questionnaire as the primary efficacy endpoint failed to show a statistically significant treatment effect of droxidopa over placebo. But a *post hoc* analysis using the same primary efficacy endpoint as study 301 showed a treatment difference of 1.11 units in OHQ composite score (p=0.013). The primary objective of the long term extension studies 303 and 304 was to assess the durability of NOH symptom relief with droxidopa. An efficacy analysis from the randomized withdrawal period at the end of study 303 did not show a clear treatment benefit favoring droxidopa over placebo (treatment difference of 0.33 units on OHQ composite, p=0.438).

Overall, the clinical development program for droxidopa demonstrated statistically significant treatment benefit only in its pivotal efficacy study 301, while the supportive efficacy study 302 showed a treatment benefit in a *post hoc* analysis. It is also not clear whether the observed treatment effect size of 0.9 units on OHQ composite score is clinically significant (please see the SEALD endpoint review by Dr. Elektra

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Papadopoulos DARRTS date 24-January-2012 for details). However, the observed treatment effect in the withdrawal phase could be underestimated as the placebo group did not worsen significantly. The dose response data during the titration phase showed higher treatment effect but the absence of placebo arms does yield an estimate of treatment effect during the titration phase. The long term extension trial 303, which had a withdrawal phase similar to study 302, also did not show a clear treatment benefit with droxidopa over placebo. However, these trials (303 and 304) were not designed to demonstrate treatment effectiveness. So the focus of our review is to evaluate whether droxidopa has any effect on NOH symptoms or it affects blood pressure to mediate its therapeutic effect in NOH patients.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 203-202. The CPB information provided is adequate to provide labeling recommendations for droxidopa. The NDA submission can be approved for NOH indication from a clinical pharmacology perspective, provided the available toxicology information on DOPAL is adequate and the observed effect size in orthostatic hypotension questionnaire (OHQ) composite scores in the Phase III trials are considered clinically meaningful.

The Office has the following specific recommendation:

- The Office of Scientific Investigations (OSI), which performed clinical and bioanalytical site inspections for pivotal bioequivalence (BE) study 101, concludes that the bioanalytical part of the pivotal BE evaluation between 3 x 100 mg capsules (phase III formulation) and 1 x 300 mg capsules (proposed new formulation) is not reliable (Ref. Memorandum to file by Dr. Jangik I Lee, DARRTS date 24-January 2012). Therefore, the BE results from this study is not acceptable and the new 300 mg capsule formulation cannot be approved based on the above BE study.

1.2 Post Marketing Requirements/Commitments

Since droxidopa and its metabolites are predominantly renally cleared, a dedicated renal impairment study to assess their exposure in renal impairment (mild, moderate, severe and ESRD) relative to subjects with normal renal function should be required. (Note: The sponsor is currently conducting this study and expects to submit the report post-approval)

2. SUMMARY OF OCP FINDINGS

2.1 Background

Chelsea Therapeutics, Inc. is seeking approval for droxidopa for the treatment of symptomatic NOH in patients with primary autonomic failure, dopamine β-hydroxylase deficiency and non-diabetic autonomic neuropathy. Droxidopa was granted orphan drug status and fast track designation for the treatment of symptomatic NOH in the US. The only drug treatment option for the symptomatic NOH indication at this time in US is midodrine, which received accelerated approval in 1996. Since the required confirmatory clinical efficacy trials were not yet completed for midodrine, FDA proposed withdrawing its approval in 2010.

2.2 Current Submission

The current NDA is supported by one pivotal efficacy trial, one supportive phase III study, two long term extension studies in NOH patients, a 24-hour ABPM study (Studies 301-305) and a PK/food effect/pivotal BE study (Study 101). The drug development program also consists of 4 Phase II clinical studies conducted before the current sponsor acquired rights to droxidopa in addition to pharmacokinetic (PK) studies in healthy human volunteers and metabolism studies. There were no dedicated renal or hepatic impairment studies or drug-drug interaction studies in their development program. A population PK/PD analysis and a thorough QT study (Study 102) were also included in the submission.

2.3 Pharmacokinetics

- Droxidopa is an orally administered, synthetic catecholamine acid analogue that is converted to norepinephrine (NE).
- The pharmacokinetics for droxidopa is nearly dose-proportional from 100 to 600 mg.
- Doxidopa's average elimination half-life is 2.5 hours. The proposed dosing regimen requires droxidopa to be administered every 4 hours during the day.
- The plasma protein binding for droxidopa is concentration dependent (decreases from 75% to 25% with increase in concentrations from 0.1 to 10 ug/ml).
- Droxidopa crosses blood brain barrier in animals and humans.
- The major active metabolite of droxidopa is norepinephrine. Other metabolites identified in humans and animals include methylated droxidopa (3-OM-DOPS), vanillic acid (VA) and protocatechuic acid (PA). These metabolites are reported to have some vasomotor activity.
- Approximately 70% of droxidopa and its metabolites are excreted in urine in animal studies.
- Droxidopa is metabolized by non-CYP mediated pathways and involves catecholamine systems in its metabolism. *In vitro* studies indicate that droxidopa has low CYP induction or inhibition potential.
- Moderate food effect for the final marketing image formulation was observed (AUC and C_{max} decrease by 20% and 35% respectively, with high fat meal).

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2.4 Exposure-Response Relationships

2.4.1 Dose dependent effect on blood pressure

Blood pressure response with droxidopa is important both for efficacy and safety. Droxidopa exhibited dose-dependent increase in systolic blood pressure during the open-label dose-titration phase in the Phase III study 302. The blood pressure effect of droxidopa was further confirmed in the pivotal efficacy trial 301 and in the 24-hour ABPM study 305. On an average approximately 8 mmHg and 5 mmHg increase in 24 hr average for systolic (SBP) and diastolic blood pressures (DBP) respectively were observed study 305. In Study 301, patients receiving droxidopa experienced a mean increase of 7.3 mmHg ($p<0.001$) in standing SBP compared to placebo between randomization and end of study. It should be noted that the blood pressure effect of droxidopa was not significant in the double-blind withdrawal phase of Study 302.

From a safety perspective, the potential for supine hypertension was evaluated in the ABPM study. There is an overall increase in BP profiles with droxidopa compared to placebo. The changes in BP with droxidopa between nocturnal and diurnal periods were comparable.

2.4.2 Dose dependent effect on NOH symptoms

The treatment effect of droxidopa on NOH symptoms were measured using orthostatic hypotension questionnaire (OHQ) individual components and as a composite score. The phase III trials (301 and 302) included an open-label dose titration phase to attain individualized doses of droxidopa, where doses were titrated from 100 mg TID to 600 mg TID over a 14 day period based on NOH symptom relief and BP response. Droxidopa exhibited dose dependent change in item 1 (dizziness, lightheadedness, feeling of fainting/blacking out), one of the predominant symptoms of the disease during this dose-titration phase. A total of 263 patients were randomized after the titration phase in these two trials and had a mean change of about -5.0 units for item 1 score between the baseline visit and end of titration.

2.5 Intrinsic Factors

2.5.1 Body weight, Sex and Age

No dose adjustment is required based on body weight, sex or age.

2.5.2 Renal Impairment

Studies in animals indicate that up to 70% of droxidopa and its metabolites are renally eliminated. The current NDA does not have a dedicated renal impairment study. However, the phase III program included NOH patients with mild and moderate renal impairment and dose titration in these studies seems to be unaffected by renal function status. Irrespective of the renal function, approximately 30% of the patients received the highest dose of 600 mg TID. The adverse event profiles in patients with mild/moderate renal impairment were similar to those with normal renal function. **Therefore, no dose adjustment is recommended for mild and moderate renal impairment.**

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2.5.3 Hepatic impairment

The current NDA has no dedicated hepatic impairment study for droxidopa. Since the metabolism of droxidopa is not CYP-mediated and involves catecholamine systems, it is unlikely that mild to moderate hepatic impairment will affect its exposure. Also, hepatic function markers like AST, ALT, alkaline phosphatase and total bilirubin did not influence exposure to droxidopa. **Hence no dose adjustment is recommended in patients with mild or moderate hepatic impairment.**

2.5.4 Pediatrics

The PK of droxidopa in children has not been studied.

2.6 Drug-Drug Interactions

- The *in vivo* PK interactions of droxidopa with other drugs were not evaluated in this NDA. The phase III trials allowed concomitant use of drugs like carbidopa/levodopa, dopamine agonists, MOA-B and COMT inhibitors for patients with Parkinson's disease. DOPA decarboxylase inhibitors increased the exposure of droxidopa by about 2-fold, but there was no significant changes in associated adverse events. There may be loss of efficacy from droxidopa if co-administered with dopa decarboxylase inhibitors. Initiation of Parkinson's therapy or major changes in dose to existing Parkinson's medication (*ie*, dopa decarboxylase inhibitors) may however warrant dose adjustments to droxidopa and dose should be titrated as appropriate. **The label should incorporate language indicating the above observation.**

2.7 Biopharmaceutics

- The phase III program for droxidopa used the final market image (FMI) formulations of 100 mg and 200 mg capsules. The sponsor plans to introduce a new 300 mg capsule strength to market in an effort to reduce the pill burden. (b) (4) Therefore, bioequivalence was demonstrated between 3 x 100 mg FMI capsules and 1 x 300 mg new strength capsules in a pivotal BE study. However, the inspection report of the clinical and bioanalysis sites from OSI suggests that bioanalysis in this study is unreliable (Ref. Memorandum to file by Dr. Jangik I Lee, DARRTS date 24-January 2012). **Hence the new strength of 300 mg capsule cannot be approved at this time.**

- A high fat meal decreases AUC and C_{max} of droxidopa by 20% and 35% respectively. The C_{max} was delayed by 2 hours with high fat meal compared to fasting. Since the phase III trials were conducted without any food restrictions, the moderate food effects observed with the FMI formulation is considered as not clinically significant.

3. QUESTION BASED REVIEW

3.1 General Attributes

3.1.1 Regulatory History

Droxidopa is an orally administered, synthetic amino acid analogue that is converted to norepinephrine by endogenous DOPA decarboxylase enzyme found in many tissues and autonomic nerve terminals and is a substrate for the COMT pathway. Chelsea Therapeutics, Inc. is seeking approval for droxidopa for the treatment of symptomatic NOH in patients with primary autonomic failure, dopamine beta hydroxylase deficiency and non-diabetic autonomic neuropathy. Patients will have their dose titrated to an optimal dosage with individualized doses ranging from 100 to 600 mg three times daily (TID). Droxidopa was approved in Japan in 1989 for the treatment orthostatic hypotension, syncope and dizziness on standing up in familial amyloid polyneuropathy and multiple system atrophy and for the treatment of freezing phenomenon and dizziness on standing up in Parkinson's disease. Droxidopa was granted orphan drug status and fast track designation for the treatment of symptomatic NOH in the US. The only drug treatment option for the NOH indication in US at this time is midodrine (accelerated approval in 1996). In 2010 FDA proposed withdrawing the approval to midodrine as the required confirmatory clinical efficacy trials were not yet completed.

3.1.2 Drug Substance

Droxidopa ($C_9H_{11}NO_5$) or L-threo-Droxidopa (INN abbreviated name) is (-)-(2S,3R)-2-Amino-3-(3,4-dihydroxyphenyl)-3-hydroxypropionic acid (IUPAC name) and has a molecular weight of 213.19 (Figure 1).

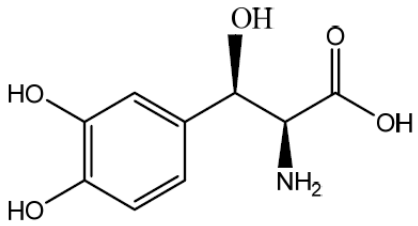

Figure 1 Structural formula of droxidopa

It is a white to off-white odorless powder, slightly soluble in water (~1.9 mg/mL), practically insoluble in organic solvents like ethanol or acetonitrile and sparingly soluble (~14 mg/mL) in 0.1 mol/L hydrochloric acid. Droxidopa has pKa of 8.78, LogP of 0.07 (b) (4)

3.1.3 What are the proposed mechanism of action and therapeutic indication?

Droxidopa is indicated for the treatment of symptomatic NOH in patients with primary autonomic failure, dopamine β-hydroxylase deficiency and non-diabetic autonomic neuropathy.

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Orthostatic hypotension is defined as a reduction of systolic blood pressure (BP) of ≥20 mmHg or diastolic BP of ≥ 10 mmHg within 3 minutes of standing. Orthostatic hypotension may be symptomatic or asymptomatic. Therefore, the primary objective of NOH treatment is to minimize the reduction in BP upon standing.

The exact mechanism of action of droxidopa is not known. Droxidopa is a synthetic amino acid analog that is metabolized through the catecholaminergic metabolism system and releases norepinephrine (NE) in addition to several other metabolites. In humans droxidopa treatment results in a transient increase in serum levels of NE (<1 ng/ml). NE increases blood pressure by inducing peripheral arterial and venous vasoconstriction and also affects the central nervous system. Droxidopa crosses blood-brain barrier and it is proposed that droxidopa exerts its effect on NOH via acting both peripherally and centrally through NE release.

3.1.4 What are the current treatments available for the proposed indication?

The only FDA approved drug at this time for the treatment of symptomatic NOH is midodrine. However, in 2010 FDA proposed withdrawing midodrine from the market as the required confirmatory clinical efficacy and safety trials were not yet complete. Other treatment options include life style modifications involving slowly getting up, avoiding dehydration by drinking plenty of fluids, small meals, elevating head of bed, and using compression stockings or abdominal bands.

3.1.5 What are the proposed dosages and route of administration?

Droxidopa is available as immediate release, oral capsule formulation in three strengths: 100, 200 and 300 mg (proposed new strength). However, the 300 mg capsule strength cannot be approved at this time due reliability issues with its BE study. Patients will have their dose titrated to an optimal dosage with individualized dosing regimens ranging from 100 to 600 mg three times daily (TID). The dose should be taken at 4 hours intervals during the day.

3.2 General Clinical Pharmacology

3.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The current NDA is supported by 5 completed phase III trials in NOH patients (Studies 301-305) and a PK/food effect/pivotal BE study (Study 101). The drug development program also consists of 4 Phase II clinical studies conducted before the current sponsor acquired droxidopa in addition to single and multiple dose PK studies in healthy human volunteers and metabolism studies. There were no dedicated renal and hepatic impairment studies, or drug-drug interaction studies in the development program. A population PK/PD analysis and a thorough QT study (Study 102) were also included in the submission.

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3.2.2 Were the correct moieties identified and properly measured to assess clinical pharmacology?

The sponsor measured plasma concentrations of droxidopa and its metabolites 3-OM-DOPS and NE in plasma. They also measured vanillic acid, protocatechuic acid and their conjugates in human urine in a phase I clinical trial. There was no mass balance study as part of the NDA submission and the urinary excretion of all these analytes in humans accounts for only 44% (corrected for the molecular weight) of a 300 mg single oral dose of droxidopa. Since droxidopa is metabolized by the catecholamine pathway, it is likely to generate several metabolites in addition to those identified above. One such metabolite is 3,4-dihydroxyphenyl acetaldehyde (DOPAL) which is reported to have neurotoxicity in animals. The pharmacology and toxicology review team has raised concerns about DOPAL which may be formed *in vivo* from droxidopa.

The pharmacodynamics/efficacy of droxidopa was measured in terms of periodic blood pressure measurements and by using orthostatic hypotension questionnaire (OHQ).

3.2.3 What are the key features of the phase III trials of droxidopa?

The phase III development program for droxidopa for symptomatic NOH includes a pivotal efficacy trial (301), a supportive study (302) and a long term extension study (303) in addition to an ABPM study (305) and long-term safety extension study (304). Studies 301 and 302 had open label dose-titration phase to attain individualized doses before starting the randomized, blinded phase of the trial. The phase III study designs for 301 and 302 are illustrated in Figure 2 and Figure 3.

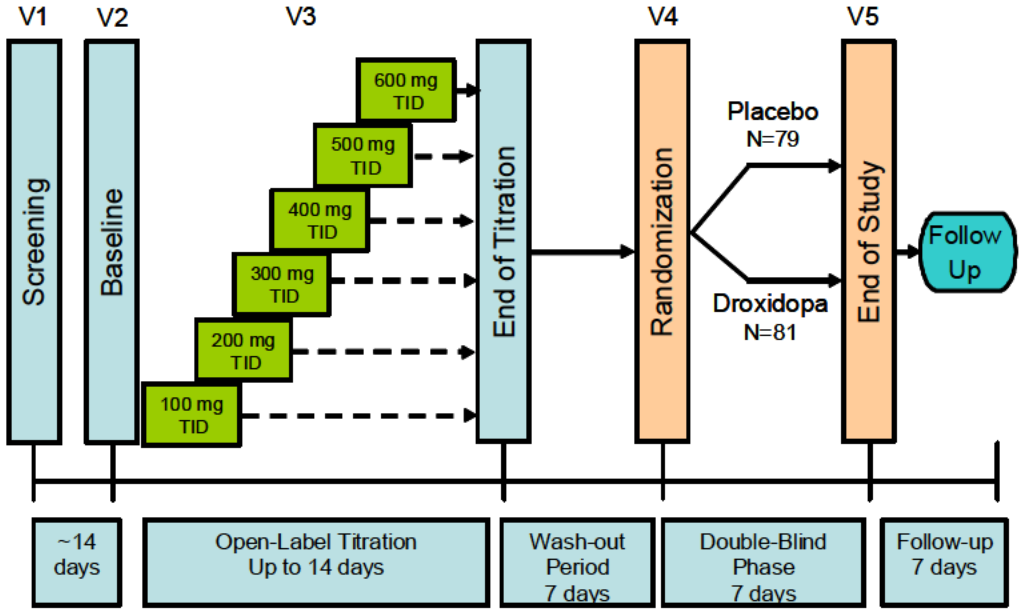

Figure 2 Induction design for study 301: There is an open-label dose-titration phase followed by one week wash-out period before randomization to one-week double-blind treatment phase.

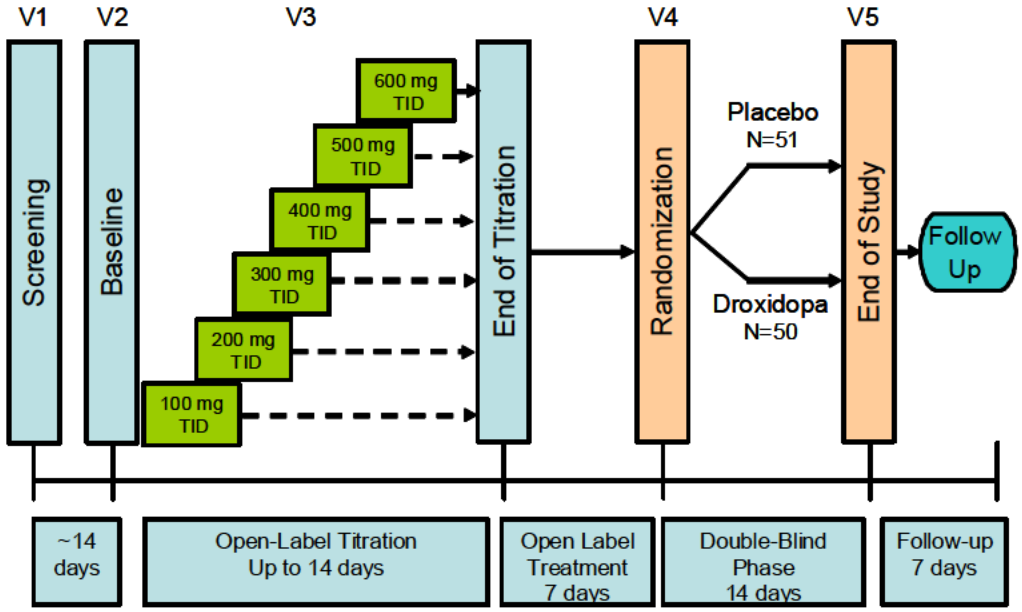

Figure 3 Withdrawal design for study 302: There is an open-label dose-titration phase followed by one week maintenance period with individualized doses of droxidopa before randomization to a two-week, double-blind withdrawal phase.

The efficacy was assessed by using a composite orthostatic hypotension questionnaire (OHQ) based scoring system. The OHQ has two components: Orthostatic hypotension symptom assessment questionnaire (OHSA) and orthostatic hypotension daily activity scale (OHDAS). OHSA involves a 6-item inventory of classic NOH symptoms (Table 1). Each item was scored 0 to 10, with higher scores indicating greater severity. A composite OHSA score was calculated by taking average symptom rating score for all items with a score of 1 or more at baseline visit.

Table 1 Individual components of OHSA questionnaire

OHSA	Item 1	Dizziness, lightheadedness, feeling faint/blacking out
	Item 2	Problems with vision such as blurring etc.
	Item 3	Generalized weakness
	Item 4	Fatigue
	Item 5	Trouble concentrating
	Item 6	Head/neck discomfort

OHDAS involves 4 questions about the impact of NOH symptoms on a patient's ability to conduct activities of daily life, with rating scales from 0 (no interference) to 10 (complete interference), with lower score indicating greater ability to perform physical activities (Table 2). A global OHDAS composite score was calculated as the average rating from all 4 items.

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Table 2 Individual components of OHDAS questionnaire

OHDAS	Item 1	Activities involving standing for a short time
	Item 2	Activities involving standing for a long time
	Item 3	Activities involving walking for a short time
	Item 4	Activities involving walking for a long time

The OHQ composite score is the mean of composite OHSA and OHDAS. The primary efficacy outcome for study 301 was the mean change in OHQ composite score from randomization to end of study in the blinded phase. Study 302 used only the item 1 of OHSA as the primary efficacy variable. The observed treatment effect for 301 and 302 for OHQ composite score were 0.9 (p=0.003) and 1.11 (p=0.013, *post hoc* analysis) respectively, favoring droxidopa over placebo. The treatment difference for OHSA item 1 from randomization to end of study for 301 and 302 were 1.3 (p<0.001) and 0.6 (p=0.509) respectively, favoring droxidopa. Details of the OHSA item 1 scores at different stages of study 301 and 302 are provided in Table 3 and Table 4. In trial 301 (induction design) patients treated with droxidopa showed an average improvement of ~3.5 unit on OHSA item 1 from their baseline measurement of ~6.5 (Table 3). However, the assessment of OHSA item 1 may be different during dose-titration (which is performed daily) and during randomization or end of study visit where patients were given OHQ scores based on a recall period of few days (SEALD endpoint review by Dr. Elektra Papadopoulos, DARRTS date 24-January-2012).

Table 3 Average OHSA Item 1 scores at different stages of study 301

Treatment/Visit	Placebo (N~80)			Droxidopa (~82)		
	OHSA Item 1	CFBL	CFRnd	OHSA Item 1	CFBL	CFRnd
Baseline	6.2 (2.4)	-	-	6.5 (2.1)	-	-
EOT	1.4 (1.9)	-4.8 (2.6)	-	1.3 (1.9)	-5.2 (2.4)	-
Rnd	5.4 (2.9)	-0.8 (2.0)	-	5.4 (2.5)	-1.1 (2.0)	-
EOS	4.3 (3.1)	-1.9 (2.7)	-1.1 (2.6)	3.0 (2.7)	-3.5 (2.7)	-2.4 (3.2)

EOT-End of titration, Rnd-Randomization, EOS-End of study, CFBL-Change from baseline, CFRnd-Change from randomization, Values are Mean (SD).

Table 4 Average OHSA Item 1 scores at different stages of study 302

Treatment/Visit	Placebo (N~51)			Droxidopa (~50)		
	OHSA Item 1	CFBL	CFRnd	OHSA Item 1	CFBL	CFRnd
Baseline	6.3 (2.3)	-	-	6.6 (2.0)	-	-
EOT	1.5 (2.1)	-4.9 (2.6)	-	1.5 (2.2)	-5.1 (2.4)	-
Rnd	2.1 (2.5)	-4.2 (2.3)	-	2.1 (2.2)	-4.4 (2.4)	-
EOS	4.0 (3.6)	-2.3 (3.5)	1.9 (3.2)	3.5 (3.2)	-3.1 (2.9)	1.3 (2.8)

EOT-End of titration, Rnd-Randomization, EOS-End of study, CFBL-Change from baseline, CFRnd-Change from randomization, Values are Mean (SD).

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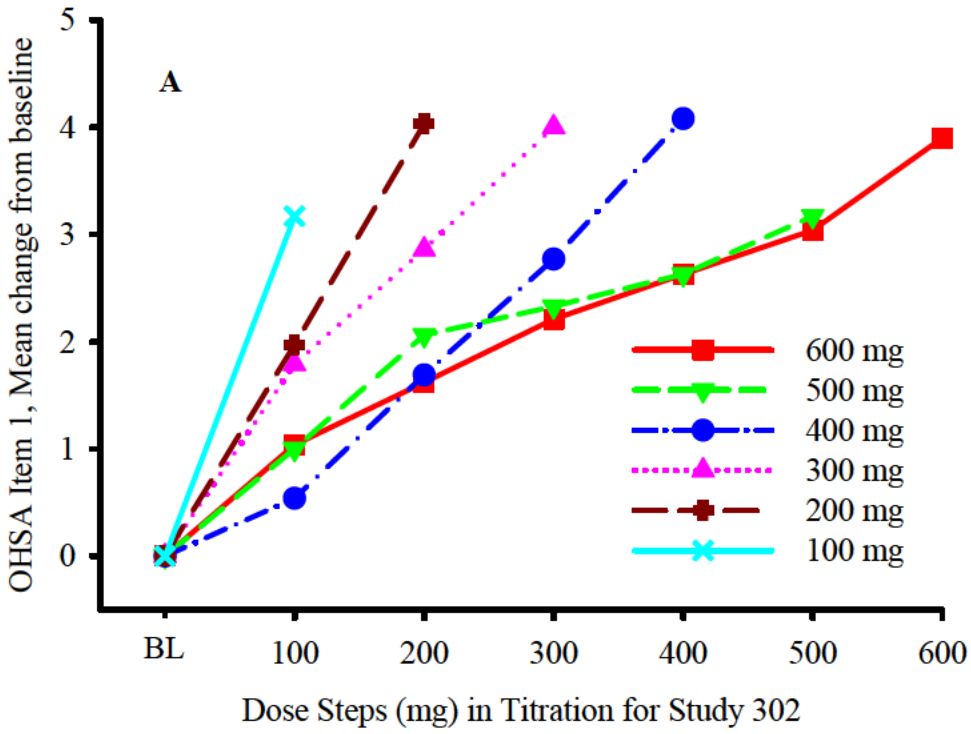
3.2.4 What are the characteristics of the exposure/dose-response relationships for efficacy?

Since the phase III studies included a dose titration phase to obtain individualized doses a clear dose-response cannot be demonstrated from the randomized, blinded-phase in sponsor's analysis. However, a dose-response was observed for item 1 of the OHSA (which is the most predominant NOH symptom) when patients were stratified by the final dose from the open-label dose titration phase of study 302, as illustrated below in Figure 4. The dose-titration phase was the same in both study 301 and 302. Additional figures and tables supporting the dose-OHSA item 1 relationships are provided in Appendix 1.



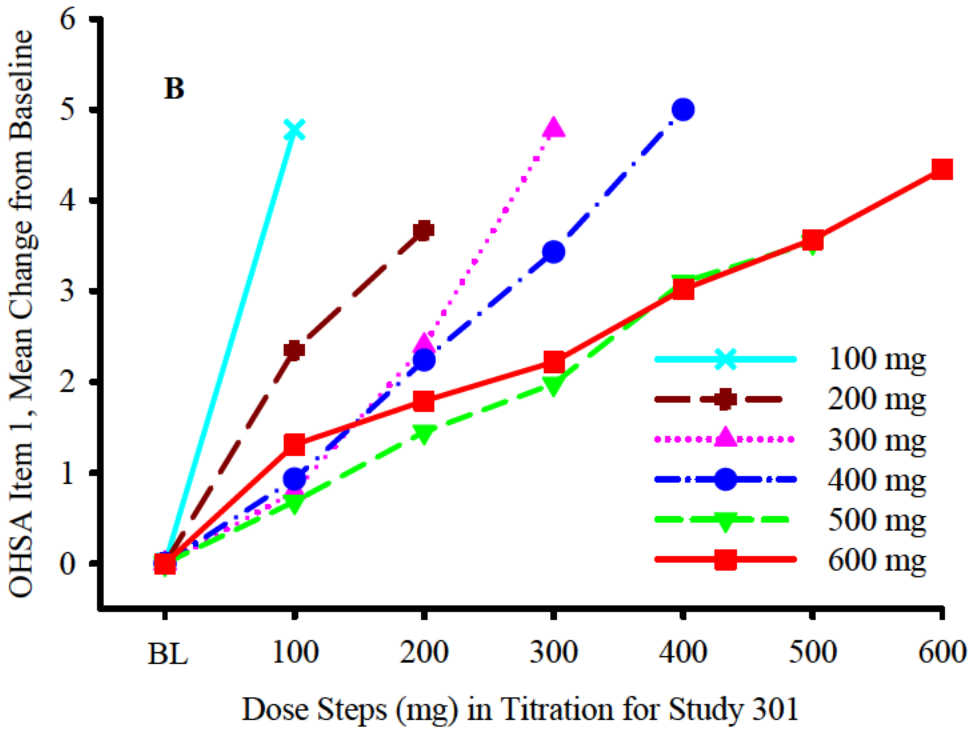


Figure 4 Mean change from baseline for OHSA item 1 (dizziness) during the open-label dose titration phase in (A) study 302 and (B) 301. Each line represents a maintenance dose group as patients are titrated, starting with 100 mg TID on the first day to the maximum dose of 600 mg TID. BL stands for baseline measurement. For example, patients who had 600 mg TID as their individualized dose went through all dose levels, 100, 200, 300, 400, 500 mg TID before reaching their optimal dose of 600 mg TID, where as patients who had 100 mg TID as their individualized dose did not try any other doses. A dose-dependent change in OHSA item 1 score is evident within each maintenance dose group.

3.2.5 Does droxidopa significantly affect blood pressure?

The primary objective of NOH treatment is to minimize the reduction in blood pressure (BP) upon standing. The proposed mechanism of action of droxidopa is elevation of BP by replenishing both central and peripheral NE levels. Droxidopa demonstrated a significant change in systolic and diastolic BP in the phase III trials. The mean change in SBP immediately before standing and on 3 minutes standing from baseline to end of dose-titration phase for patients who were randomized in phase III trials (N=263, studies 301 and 302) was 10.5 and 23.5 mmHg respectively. Similar trend was seen with DBP as well. This was further confirmed by the 24-hour ambulatory BP measurement study (305) which demonstrated an average increase in SBP and DBP of approximately 8 and 5 mmHg in NOH patients receiving individualized doses of droxidopa for four weeks.

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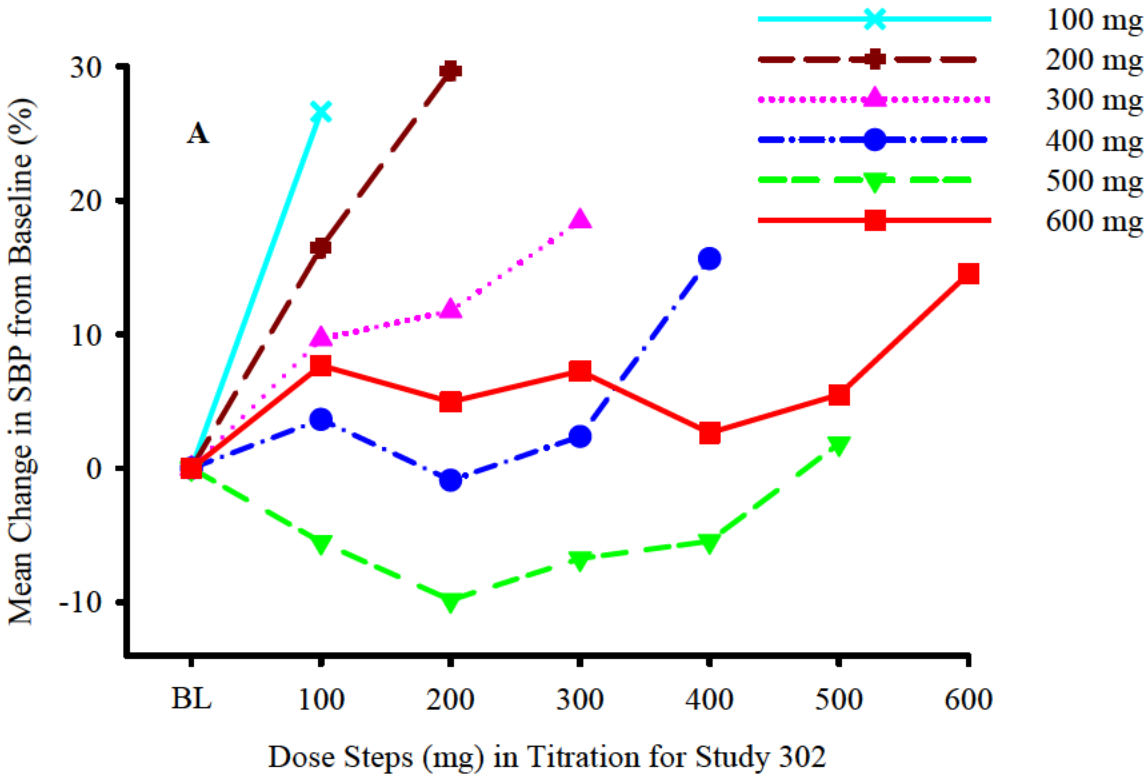
3.2.6 Is there a dose-blood pressure relationship for droxidopa?

Since droxidopa was titrated to effect (based both BP and NOH symptom score) BP response during the open-label, dose-titration phase was evaluated. A trend for dose-dependent change in SBP was observed for droxidopa during the open-label dose titration phase in study 302 and 301 (Figure 5).



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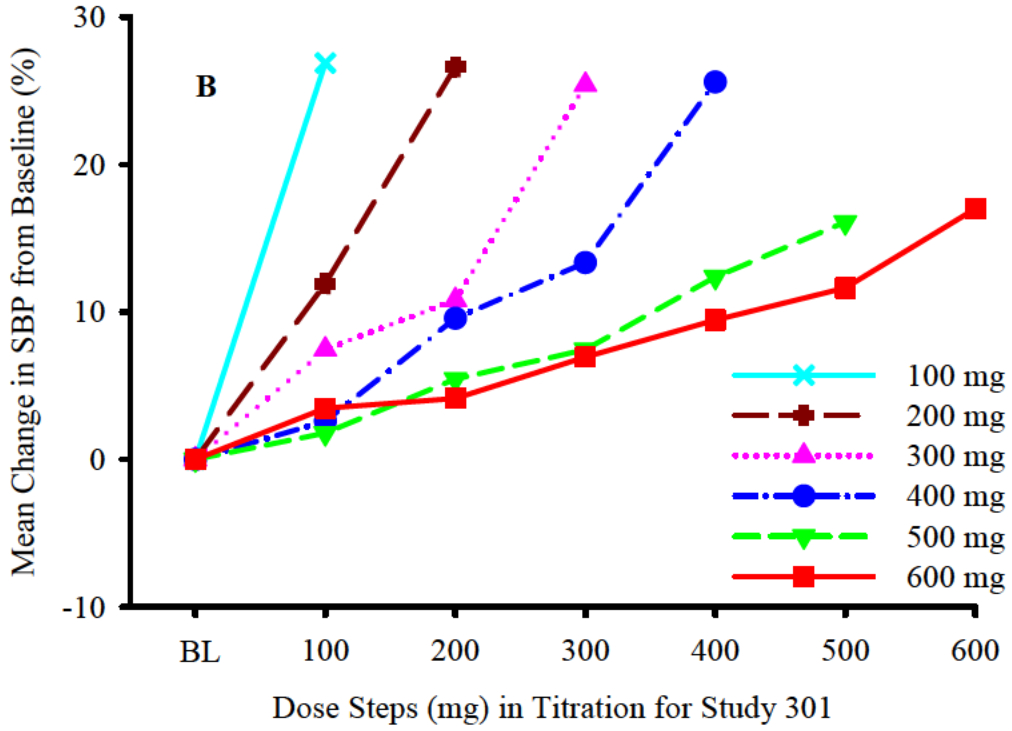

Figure 5 Mean % change from baseline in SBP during the open-label dose titration phase in (A) study 302 and (B) study 301. Each line represents a maintenance dose group as patients are titrated, starting with 100 mg TID on the first day to the maximum dose of 600 mg TID. BL stands for baseline measurement. A dose-dependent change in SBP is evident within each maintenance dose group, even though the study population includes both NOH symptom only responders and symptom as well as BP responders. The pivotal efficacy trial 301 had a similar dose titration process

3.2.7 Is there a risk for supine hypertension with droxidopa?

A major safety concern in treating orthostatic hypotension by using drugs with a potential for BP elevation is the risk of having supine hypertension, especially in the night. The 24-hour ABPM study (305) evaluated the BP profiles of 18 patients with NOH before and after receiving 4 weeks treatment with individualized doses of droxidopa. As shown below in Table 5 and Figure 6, there was no significant difference in the BP elevation with or without droxidopa treatment between diurnal (8 am to 4 pm) and nocturnal (11 pm to 5 am) periods.

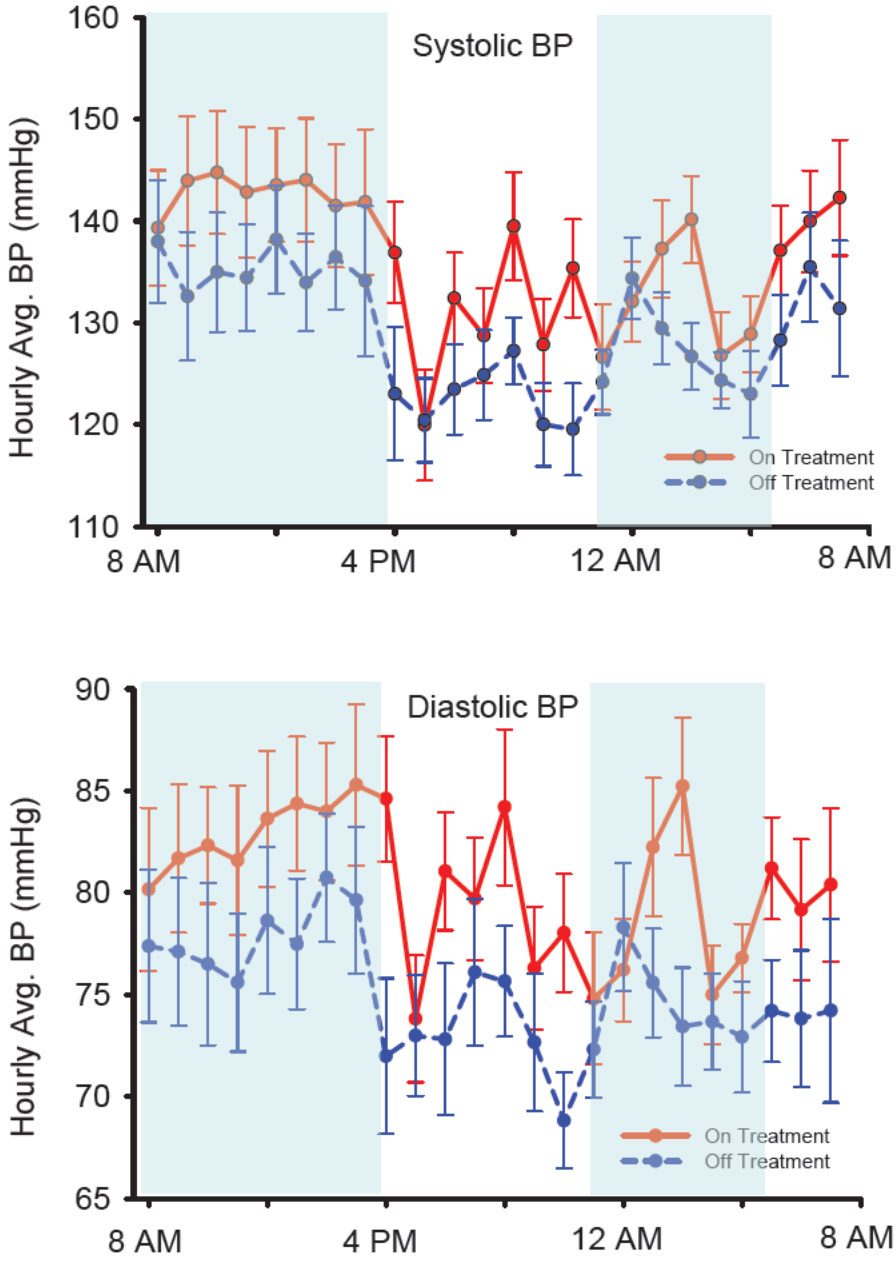

Figure 6 Hourly average systolic and diastolic BP profiles from 24-hour ABPM study (305) in NOH patients (N=18, Mean, SE) showing similar changes in diurnal (8 am to 4 pm) and nocturnal (11 pm to 5 am) BP with (on treatment, red solid line) and without (off-treatment, blue broken line) 4-weeks of droxidopa treatment at individualized dose level. Droxidopa was administered in a TID regimen during the day at 8 AM, 12 PM and 4 PM. No droxidopa dose was given in the night. Shaded regions represent diurnal and nocturnal period.

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Table 5 Average diurnal and nocturnal BP from the ABPM study 305

Average BP (mmHg)		On Treatment	Off Treatment	Change
Diurnal (8 AM-4 PM)	Systolic	131.2 (3.1)	122.8 (2.2)	8.4 (3.1)
	Diastolic	79.3 (2.1)	73.8 (1.9)	5.5 (1.8)
Nocturnal (11 PM-5 AM)	Systolic	143.3 (5.6)	135.5 (5.4)	7.8 (4.8)
	Diastolic	82.6 (.2)	77.8 (3.4)	4.8 (2.5)

Values are Mean (SD), N~18 from study 305

It is observed from studies 301 and 302 that baseline SBP may have some predictive value in assessing the risk for supine hypertension with droxidopa. Patients who experienced supine hypertension also had higher SBP at baseline (~150 mmHg vs 127 mmHg) and at screening (~163 mmHg vs 132 mmHg) than patients who did not have supine hypertension. Pre-existing hypertension should be carefully monitored while using droxidopa to minimize the risk for supine hypertension. Evaluation of patients from studies 301 and 302 who had at least one measurement of SBP>180 mmHg or DBP>110 mmHg in the orthostatic challenge test showed that they had higher mean age, more likely to be males and patients with pure autonomic failure.

3.2.8 Does droxidopa prolong the QT or QTc interval?

The sponsor performed a thorough QT study (study 102) to assess the electrophysiological effects of droxidopa. A preliminary evaluation suggests that droxidopa does not prolong QT interval. The QT Consult is pending with the Interdisciplinary Review Team for QT Studies Consultation.

3.3 PK Characteristics of the Drug and Metabolite(s)

3.3.1 What are the single dose and multiple dose PK parameters?

The PK of droxidopa was studied in single-dose (studies 20/1859-94, 20/1860-94) and multiple-dose (study 101) designs in healthy subjects. There was a dose related increase in exposure up to 600 mg dose (See Figure 7 below). The terminal elimination half-life of droxidopa ranged from 2.1 to 2.4 hours. The major metabolite 3-OM-DOPS also showed dose-dependent increase in exposure up to 600 mg dose level and had an elimination half-life of 4.7 to 5.3 hours. No dose-dependent relationship could be attributed to NE levels with droxidopa. There was no significant accumulation of droxidopa on multiple dose administration in a TID regimen (See Figure 8 below).

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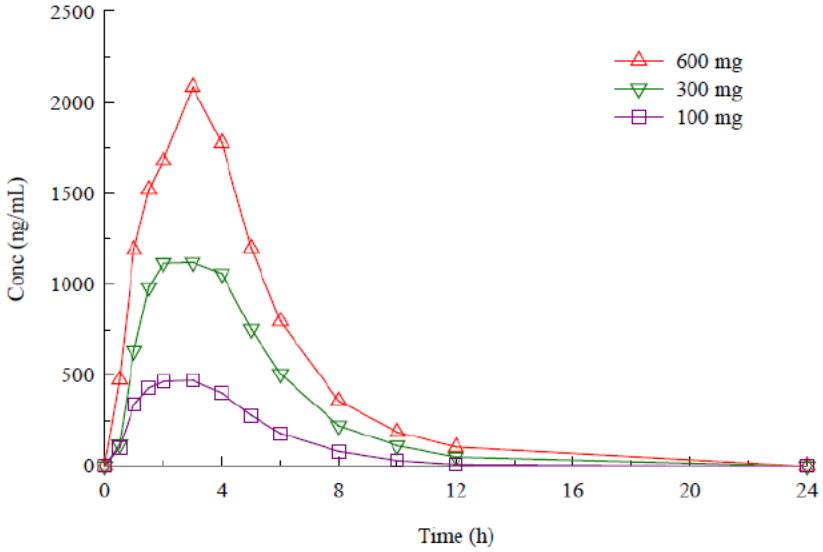

Figure 7 Average plasma concentrations of droxidopa in healthy male subjects (N=20) after oral administration of 100, 300, and 600 mg single doses administered under fasting conditions. Source: Figure 1, Study 20/1860-94

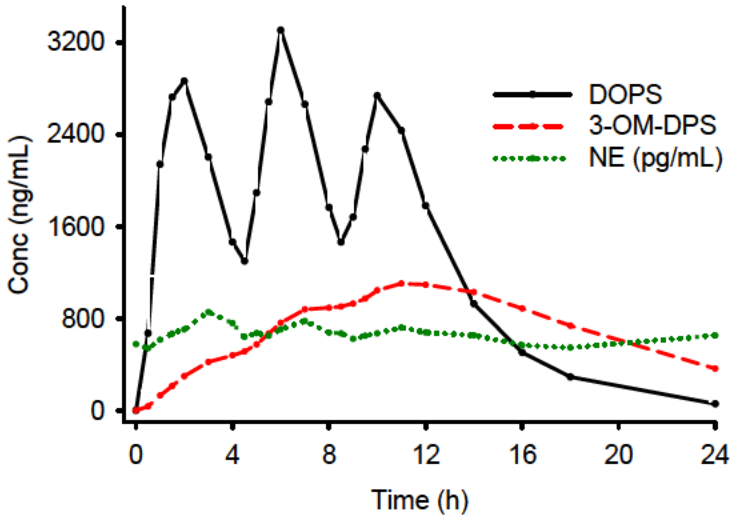

Figure 8 Average plasma concentrations of droxidopa (DOPS, black solid line) and its metabolites 3-OM-DOPS (red broken line) and NE (green dotted line) in healthy subjects (N=24, 300 mg TID dose) from phase I PK study (101). Plasma levels of NE were relatively low (expressed in pg/mL).

3.3.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The results of the population pharmacokinetic analysis indicate that the pharmacokinetics of droxidopa and 3-OM-DOPS were almost similar between healthy elderly subjects and NOH patients.

3.3.3 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose linearity/proportionality was assessed using studies 20/1859-94 and 20/1860-94 in healthy subjects. Droxidopa showed linear PK over the range of 100 to 600 mg (Figure 9). The metabolite 3-OM-DOPS showed dose-related, but less than proportional, increase in exposure with dose. The changes in NE levels in general were not dose related.

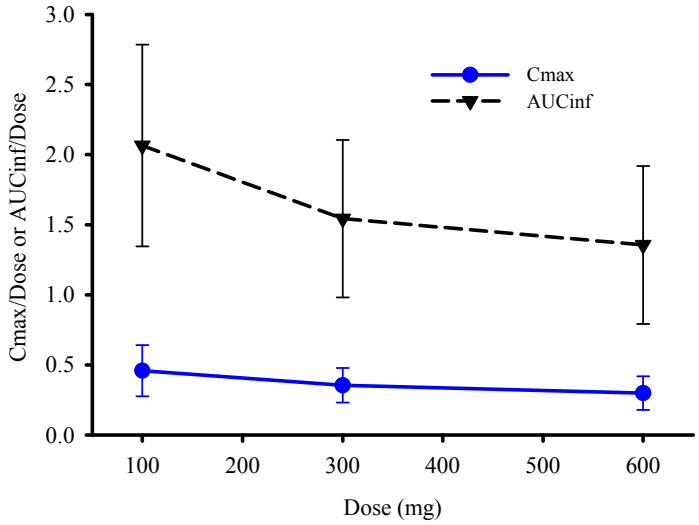

Figure 9 Relationship between dose-normalized mean C_{max} (ug/mL), AUC_{inf} (ug.h/mL) and dose (mg) after oral administration of 100, 300 and 600 mg doses in healthy subjects. Values are Mean (SD), N~20. Source: Table 7.2.2, Study 20/1860-94

3.3.4 What is the inter- and intra-subject variability of the PK parameters, and what are the major causes of variability?

The estimates of between subject variability (% CV) in apparent volume of distribution (V/F) and clearance (CL/F) were approximately 25 % (study 101, part II). The exposure (AUC) and C_{max} showed variability of approximately 30-35%. High fat meal is found to have moderate effect on exposure with C_{max} and AUC decreasing by 35% and 20% respectively.

3.3.5 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

3.3.5.1 Body weight, Sex and Age

Population PK analysis indicate that exposure to droxidopa was not significantly affected by body weight or sex. Increase in age above 65 years was associated with a decrease in apparent clearance of by 0.8% per year. There was no apparent effect of age on dose selection during the titration phase in Phase III trials. It is also notable that patients over 75 years of age showed little to no benefit following droxidopa treatment for NOH

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symptoms or BP measurements. Since droxidopa is titrated to effect, individuals not demonstrating NOH symptom relief after reaching highest dose level are expected to discontinue treatment. Therefore, no dose adjustment is required based on body weight, sex or age.

3.3.5.2 Renal Impairment

Studies in animals indicate that up to 70% of droxidopa and its metabolites are renally eliminated. The current NDA does not have a dedicated renal impairment study. The phase III program included NOH patients with mild and moderate renal impairment and dose titration seems to be unaffected by renal impairment status. Irrespective of the renal function, approximately 30% of the patients received the highest dose of 600 mg TID (See Table 6 below). The adverse event profiles in patients with renal impairment were similar to those with normal renal function in these studies.

Table 6 Distribution of individualized doses from study 302.

CrCL (mL/min)	Number of patients	% Patients in each dose (mg) group					
		100	200	300	400	500	600
<30	6	16.7	33.3	0	16.7	0	33.3
30-50	10	10	0	40	10	10	30
>50	75	9.3	22.7	14.7	10.7	10.7	32

Data from PK-PD dataset, N=91 at visit 4 randomization in study 302

Therefore, no dose adjustment is required for mild and moderate renal impairment. The sponsor has submitted a clinical trial protocol (Study NOH 103) for studying the PK of droxidopa in renal impairment on 16-November-2011. This study will include patients with mild, moderate, severe renal impairment and ESRD.

3.3.5.3 Hepatic Impairment

The current NDA has no dedicated hepatic impairment study for droxidopa. Since the metabolism of droxidopa is not CYP mediated and involves catecholamine systems, it is unlikely that mild to moderate hepatic impairment will affect its exposure. Hepatic function, assessed by AST (N=91, Mean= 20.31, Range 9-61 IU/L), ALT (N = 91, Mean = 15.52, Range 3-42 IU/L), alkaline phosphatase (N = 91, Mean = 79.87, Range 26-141 IU/L), and total bilirubin (N = 91, Mean = 9.132, Range 3.4-23.9 µmol/L, did not influence exposure to droxidopa. Hence no dose adjustment is needed in patients with mild or moderate hepatic impairment.

3.3.6 What are the characteristics of drug absorption (possible transporters and pH impact)?

Droxidopa is rapidly absorbed after oral dosing in healthy humans with peak plasma concentrations attained on an average by 2 hours post dose. Influence of pH or involvement of any transporters on absorption was not studied. High fat meal seems to have a moderate impact on droxidopa exposure with C_{max} and AUC decreasing by 35% and 20% respectively. The C_{max} was delayed by approximately 2 hours with high fat meal.

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3.3.7 What are the characteristics of drug distribution, including plasma protein binding?

Droxidopa is known to cross blood-brain barrier in both animals and humans. Droxidopa exhibits concentration dependent plasma protein binding from approximately 75% to 26% over a concentration range of 100 ng/mL to 10,000 ng/mL. Plasma protein binding of 3-OM-DOPS is reported to be very low (~1%). The estimated apparent volume of distribution of droxidopa is about 200L in humans.

3.3.8 What are the characteristics of drug metabolism?

The metabolism of droxidopa was studied in mice, rats, dogs and rhesus monkeys. The proposed metabolic pathway is illustrated below in Figure 10 and is reported to be comparable across species including humans. The primary metabolite of droxidopa in humans and animals in tissue, serum, and urine is 3-OM-DOPS. Droxidopa may be initially converted to 3-OM-DOPS by catechol-O-methyltransferase (COMT), to NE by 3,4- dihydroxyphenylalanine (DOPA) decarboxylase or to protocatechualdehyde by DOPS aldolase. These primary metabolites are further metabolized as follows: 3-OM-DOPS is converted to the secondary metabolite vanillic acid (VA) and NE is converted to the secondary metabolite 3-methoxy-4-hydroxy-phenylglycol (HMPG) by COMT and monoamine oxidase (MAO), which may then be converted to the tertiary metabolite dihydroxyphenylglycol (DHPG) by aldehyde/aldose reductase. Protocatechualdehyde appears to be highly reactive and is rapidly converted to PA by an aldehyde dehydrogenase or to a lesser degree, 3,4-dihydroxytoluene (HC) via reductive metabolism.

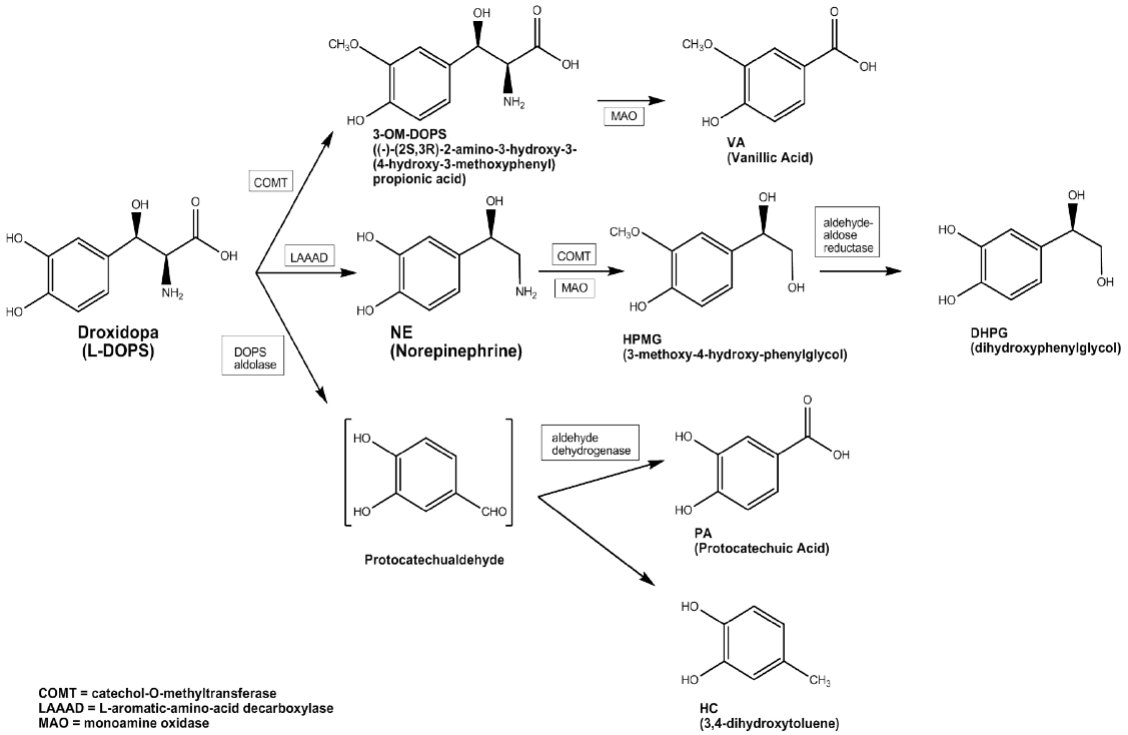

Figure 10 Proposed metabolic pathway for droxidopa. Source: Section 2.7.2, Figure 2-1, Page 10

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There was no mass balance study in humans and two additional metabolites (vanillic acid and protocatechuic acid) were estimated from human urine samples from phase I clinical studies (D-08 and E-01). Only about 44% of the total dose of 300 mg droxidopa (corrected for the molecular weight) as shown below (Figure 11) was accounted for with the parent and its metabolites or their conjugates in urine.

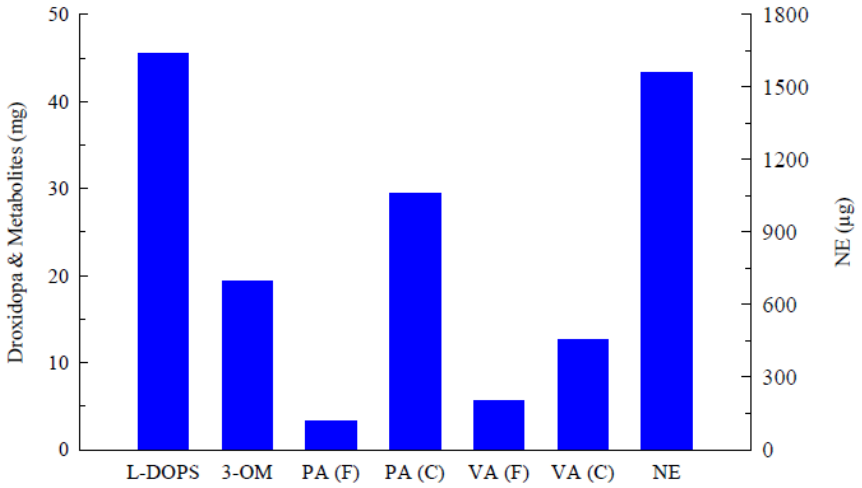

Figure 11 Average 24 hour urinary excretion of droxidopa, 3-OM-DOPS, vanillic acid (free and conjugated), protocatechuic acid (free and conjugated) and norepinephrine after oral administration of a single 300 mg dose of droxidopa in humans. Source: 2.7.2, Figure 2-4, Page 14 (Study D-08, E-01)

Since droxidopa is a substrate for the COMT pathway it is possible to have additional metabolites not identified here. One such notable metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL), which is also identified as a possible contaminant in the drug substance, is potentially neurotoxic and the Pharmacology/Toxicology review team has raised some concern about the possibility of DOPAL generated *in vivo* and its potential effects in humans.

3.3.9 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study was performed for droxidopa in humans. The major route of elimination of droxidopa and its metabolites is via kidneys in both animals and in humans. Studies in animals using ^{14}C-droxidopa showed that ~70% of the radio labeled dose was excreted in urine within 24 hours of oral dosing.

3.3.10 What is the drug-drug interaction (DDI) potential for droxidopa?

In vitro studies evaluating the effects of droxidopa on CYP1A2, 2B6, and 3A4/5 in human hepatocyte cultures indicated that drug-drug interaction potential based on CYP induction is low. The *in vitro* inhibitory effects of droxidopa on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 were also found to be low. Since droxidopa

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metabolism is non-CYP mediated and has low DDI potential there were no dedicated drug-interaction studies included in the current NDA.

The phase III program allowed concomitant medications for Parkinson's disease and the DDI potentials were evaluated only for those drugs (dopa decarboxylase inhibitors, dopamine agonists, MOA-B and COMT inhibitors) in the phase III setting for this NDA. It was observed that dopa decarboxylase inhibitors (DDC-I) resulted in a 2-fold increase in exposure to droxidopa in study 302. But there were no significant increase in treatment related adverse events in patients receiving DDC-I. The distribution of optimal doses was similar among patients not taking and those taking DDC-I (See Figure 12 below).

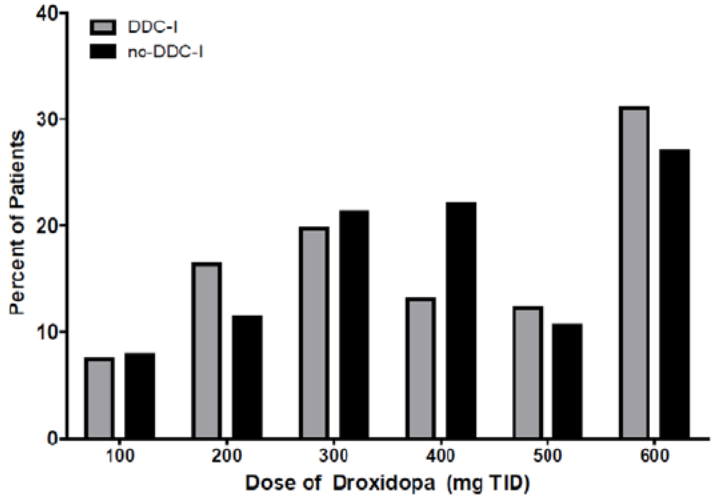

Figure 12 Dose distribution was similar in randomized patients with or without dopa decarboxylase inhibitors (DDC-I) from study 302. Source: Figure 5-4, Module 2.7.3, Page 71

Patients **not** taking DDC-I together with droxidopa showed numerically higher improvements in NOH symptoms and BP compared to patients on DDC-I (OHQ composite score of 4.2 versus 2.7 at the end of study for patients in the pivotal efficacy study 301). It should be noted that it is difficult to delineate the actual effects of DDC-I on NOH symptom relief in a phase III setting where multiple drugs are used concomitantly in a diverse patient population. A comparison of clinical efficacy in NOH patients with and without co-administered DDC-I drugs are provided in Tables 7-8.

Table 7 Average of OHSA item 1 scores (SD) with and without concomitant DDC inhibitors from study 302.

Treatment / DDC-I use	**Placebo**		**Droxidopa**	
	No DDC	**DDC use**	**No DDC**	**DDC Use**
Randomization (R)	2.9 (2.5)	1.5 (2.4)	2.5 (2.2)	1.9 (2.2)
End of Study (EOS)	5.7 (3.5)	2.8 (3.1)	4.1 (3.1)	3.0 (3.21)
Δ (R-EOS)	**-2.8 (3.1)**	**-1.3 (3.1)**	**-1.6 (2.1)**	**-1.1 (3.2)**

Withdrawal design, N~44 with no DCC inhibitor use and N~57 with DCC inhibitors

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Table 8 Average of OHSA Composite scores (SD) with and without concomitant DDC inhibitors from study 301.

Treatment / DDC-I use	Placebo		Droxidopa	
	No DDC	DDC use	No DDC	DDC Use
Randomization (R)	4.5 (2.5)	4.9 (2.2)	4.5 (2.1)	4.8 (1.9)
End of Study (EOS)	3.6 (2.8)	3.9 (2.1)	2.4 (1.9)	3.8 (2.1)
Δ (R-EOS)	**0.9 (2.1)**	**1.1 (1.7)**	**2.1 (2.1)**	**1.1 (1.9)**

Induction design, N~97 with no DCC inhibitor use and N~65 with DCC inhibitors

This observation is in agreement with the proposed mechanism of action of droxidopa, where NE formed from droxidopa by dopa decarboxylase is considered as the pharmacologically active moiety. Peripherally, DDC-I prevents the formation of NE from droxidopa, thereby reducing its pharmacological activity mediated through NE. Though the exact mechanism of action of droxidopa is not known, it is believed to act through NE both centrally and peripherally. Droxidopa crosses blood brain barrier whereas DDC-I like cardidopa do not. Therefore co-administration of DDC-I (like carbidopa) may reduce the formation of NE from droxidopa and decrease its peripheral activity without altering effects on CNS much. Though it may be beneficial from NOH therapy perspective to avoid DDC-I co-administration with droxidopa, it may not be a viable option for many patients with Parkinson's disease. Besides there were no significant increase in treatment related adverse events in patients receiving DDC-I (though exposure to droxidopa increased by 2-fold with DCC-I co-administration) and therefore no dose adjustments are required. Initiation of Parkinson's therapy or major changes in dose to existing Parkinson's medication (*ie*, dopa decarboxylase inhibitors) may however warrant dose adjustments to droxidopa and dose should be re-titrated as appropriate. Supine blood pressure should be monitored more frequently in such patients.

Since droxidopa is metabolized by MAO-B and COMT, inhibition of these enzymes may result in significant changes to exposure to droxidopa. Initiating therapy with MAO-B or COMT inhibitors may warrant dose adjustments to droxidopa.

3.4 Biopharmaceutics

3.4.1 What are the characteristics of the bioanalytical method(s) used in the clinical pharmacology studies?

The plasma concentration of droxidopa and its metabolites were estimated using two validated HPLC-MS/MS methods: (b) (4) Method and (b) (4) method (Table 9). Both methods were validated for droxidopa, 3-OM-DOPS and NE as analytes in human plasma. The accuracy and precision of the assay methods are within limits (≤20% at LOQ and ≤15% at all other QC levels) and the validation parameters reported for these two methods are acceptable.

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Table 9 Linearity ranges for the analytical methods used

Analyte	[redacted] Method*	[redacted] Method
Droxidopa	5 – 3000 ng/mL	50 – 10,000 ng/mL**
3-OM-DOPS	5 – 3000 ng/mL	10 – 600 ng/mL
NE	50 – 2500 pg/mL	20 – 2500 pg/mL

*Studies 101, 102 and 302 used [redacted] Method, **Combined linearity range

3.4.2 What is the composition of the final marketing image formulation(s) and how is it bridged to the Phase III formulation(s)?

Droxidopa capsules are formulated into three strengths: 100, 200 and 300 mg. The compositions of the capsules are listed below in Table 10.

Table 10 Composition of the final marketing image formulations of droxidopa

Ingredient	Function	mg/capsule (% w/w)		
Droxidopa	API	100 [redacted]	200 [redacted]	300 [redacted]
Mannitol	[redacted]			
Corn starch				
Magnesium stearate				
Total weight		270 (100)	370 (100)	480 (100)
Capsule size		3	2	1

API: Active pharmaceutical ingredient

The 100 and 200 mg strengths are the same as those used in the phase III clinical trials. The new 300 mg strength capsule, introduced to reduce the pill burden, [redacted] the sponsor demonstrated bioequivalence between 1x300 mg and 3x100 mg capsules in a phase I clinical study (Study 101). The geometric mean ratios and 90%CI values for C_{max} and AUC_{∞} from study 101 are well within the BE acceptance criteria as shown in Figure 13.

[redacted]

Figure 13 Results of the pivotal BE study comparing 3x100 mg and 1x300 mg capsules.

The Office of Scientific Investigations (OSI) conducted a clinical and bioanalytical site inspection for this pivotal BE study and recommended that the bioanalytical data in the

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bioequivalence part of study 101 are not reliable (Ref. Memorandum to file by Dr. Jangik I Lee, DARRTS date 24-January 2012). Therefore we cannot accept the BE results from this study that bridges 100 mg phase III formulation with the proposed new 300 mg capsule formulation and the new 300 mg capsule cannot be approved at this time.

APPENDIX-1 Tables and Figures not included in the QBR

Table 1. Mean percentage change in OHSA Item 1 (Dizziness) from baseline from the open-label dose-titration phase of study 302 (withdrawal design)

Dose Group (mg)	Visit Number	Dose Step (mg)	N	Mean	Median	SD	SE
100	2	0	18	0.00	0.00	0.00	0.00
100	3.1	100	18	59.31	84.52	50.69	11.95
200	2	0	32	0.00	0.00	2.95	0.52
200	3.1	100	31	29.59	28.57	31.96	5.74
200	3.2	200	29	61.81	100.00	49.91	9.27
300	2	0	35	0.00	0.00	0.00	0.00
300	3.1	100	34	26.11	22.50	32.99	5.66
300	3.2	200	35	43.72	40.00	37.79	6.39
300	3.3	300	37	59.93	71.43	48.78	8.02
400	2	0	13	0.00	0.00	0.00	0.00
400	3.1	100	13	5.78	12.50	39.94	11.08
400	3.2	200	13	34.34	25.00	41.59	11.54
400	3.3	300	13	46.66	57.14	47.77	13.25
400	3.4	400	13	76.24	100.00	35.17	9.75
500	2	0	35	0.00	0.00	0.00	0.00
500	3.1	100	36	8.48	18.33	50.02	8.34
500	3.2	200	35	30.21	20.00	44.30	7.49
500	3.3	300	36	37.05	30.95	41.78	6.96
500	3.4	400	35	43.19	40.00	46.55	7.87
500	3.5	500	36	50.20	60.00	44.84	7.58
600	2	0	49	0.00	0.00	21.43	3.06
600	3.1	100	50	14.65	10.56	34.93	4.94
600	3.2	200	50	22.39	20.00	42.03	5.94
600	3.3	300	48	31.37	26.79	41.53	5.99
600	3.4	400	49	38.54	33.33	38.46	5.49
600	3.5	500	48	46.33	41.43	39.02	5.63
600	3.6	600	50	60.66	68.75	44.21	6.25

Visit 2 and 3 are baseline and titration visits, respectively

Reference ID: 3076920

Table 2. Mean percentage change in OHSA Item 1 (Dizziness) from baseline from the open-label dose-titration phase of study 301 (Induction design)

Dose Group (mg)	Visit Number	Dose Step (mg)	N	Mean	Median	SD	SE
100	2	0	9	0.00	0.00	0.00	0.00
100	3.1	100	9	78.48	100.00	40.93	13.64
200	2	0	20	0.00	0.00	0.00	0.00
200	3.1	100	20	43.04	46.43	32.23	7.21
200	3.2	200	21	66.49	100.00	40.01	8.73
300	2	0	43	0.00	0.00	0.00	0.00
300	3.1	100	43	11.59	11.11	22.94	3.50
300	3.2	200	43	38.37	40.00	29.12	4.44
300	3.3	300	45	81.19	100.00	34.36	5.12
400	2	0	45	0.00	0.00	0.00	0.00
400	3.1	100	49	12.49	11.11	25.43	3.79
400	3.2	200	48	35.93	33.33	25.00	3.69
400	3.3	300	48	55.63	66.67	33.64	4.96
400	3.4	400	49	70.52	100.00	81.92	12.21
500	2	0	40	0.00	0.00	0.00	0.00
500	3.1	100	41	9.78	0.00	22.68	3.54
500	3.2	200	40	19.62	25.00	35.70	5.64
500	3.3	300	40	28.83	30.95	41.39	6.55
500	3.4	400	40	44.31	56.35	38.78	6.13
500	3.5	500	40	55.39	71.43	52.66	8.43
600	2	0	96	0.00	0.00	3.42	0.35
600	3.1	100	98	12.54	10.00	57.39	5.83
600	3.2	200	97	26.80	25.00	32.46	3.33
600	3.3	300	95	28.73	26.79	46.75	4.82
600	3.4	400	96	41.28	50.00	47.12	4.83
600	3.5	500	96	50.58	57.14	54.00	5.54
600	3.6	600	97	62.18	71.43	40.89	4.19

Visit 2 and 3 are baseline and titration visits, respectively

Reference ID: 3076920

Table 3. Mean change in OHSA Item 1 (Dizziness) from baseline from the open-label dose-titration phase of study 302 (Withdrawal design)

Dose Group (mg)	Visit Number	Dose Step (mg)	N	Mean	Median	SD	SE
100	2	0	18	0.00	0.00	0.00	0.00
100	3.1	100	18	3.17	3.50	2.85	0.67
200	2	0	32	0.00	0.00	0.00	0.00
200	3.1	100	31	1.97	1.00	2.47	0.44
200	3.2	200	29	4.03	3.00	3.67	0.68
300	2	0	34	0.00	0.00	0.00	0.00
300	3.1	100	34	1.79	1.00	2.24	0.38
300	3.2	200	35	2.86	3.00	2.33	0.39
300	3.3	300	37	4.00	4.00	2.99	0.49
400	2	0	13	0.00	0.00	0.00	0.00
400	3.1	100	13	0.54	1.00	2.03	0.56
400	3.2	200	13	1.69	1.00	2.25	0.62
400	3.3	300	13	2.77	2.00	2.52	0.70
400	3.4	400	13	4.08	4.00	2.43	0.67
500	2	0	35	0.00	0.00	0.00	0.00
500	3.1	100	36	1.00	1.00	2.74	0.46
500	3.2	200	35	2.06	1.00	2.84	0.48
500	3.3	300	36	2.33	2.00	2.85	0.47
500	3.4	400	35	2.63	3.00	2.96	0.50
500	3.5	500	35	3.17	3.00	3.06	0.52
600	2	0	49	0.00	0.00	0.00	0.00
600	3.1	100	50	1.04	1.00	2.16	0.31
600	3.2	200	50	1.62	1.50	2.71	0.38
600	3.3	300	48	2.21	2.00	2.63	0.38
600	3.4	400	49	2.63	2.00	2.75	0.39
600	3.5	500	48	3.04	3.00	2.67	0.39
600	3.6	600	50	3.90	4.00	2.96	0.42

Visit 2 and 3 are baseline and titration visits, respectively

Reference ID: 3076920

Table 4. Mean change in OHSA Item 1 (Dizziness) from baseline from the open-label dose-titration phase of study 301 (Induction design). Visit 2 and 3 are baseline and titration visits, respectively

Dose Group (mg)	Visit Number	Dose Step (mg)	N	Mean	Median	SD	SE
100	2	0	9	0.00	0.00	0.00	0.00
100	3.1	100	9	4.78	5.00	3.27	1.09
200	2	0	20	0.00	0.00	0.00	0.00
200	3.1	100	20	2.35	2.50	1.93	0.43
200	3.2	200	21	3.67	3.00	2.90	0.63
300	2	0	43	0.00	0.00	0.00	0.00
300	3.1	100	43	0.79	1.00	1.28	0.20
300	3.2	200	43	2.40	2.00	1.85	0.28
300	3.3	300	45	4.78	5.00	2.58	0.38
400	2	0	45	0.00	0.00	0.00	0.00
400	3.1	100	45	0.93	1.00	1.25	0.19
400	3.2	200	46	2.24	2.00	1.79	0.26
400	3.3	300	46	3.43	3.50	2.33	0.34
400	3.4	400	45	5.00	5.00	3.25	0.49
500	2	0	40	0.00	0.00	0.00	0.00
500	3.1	100	41	0.68	0.00	1.29	0.20
500	3.2	200	40	1.45	1.00	1.80	0.28
500	3.3	300	40	1.98	2.00	1.98	0.31
500	3.4	400	40	3.10	3.00	2.27	0.36
500	3.5	500	39	3.54	3.00	3.28	0.53
600	2	0	95	0.00	0.00	0.00	0.00
600	3.1	100	97	1.31	1.00	2.30	0.23
600	3.2	200	95	1.79	1.00	2.28	0.23
600	3.3	300	94	2.22	2.00	2.57	0.27
600	3.4	400	95	3.02	3.00	2.67	0.27
600	3.5	500	95	3.57	3.00	2.82	0.29
600	3.6	600	95	4.34	4.00	2.75	0.28

Reference ID: 3076920

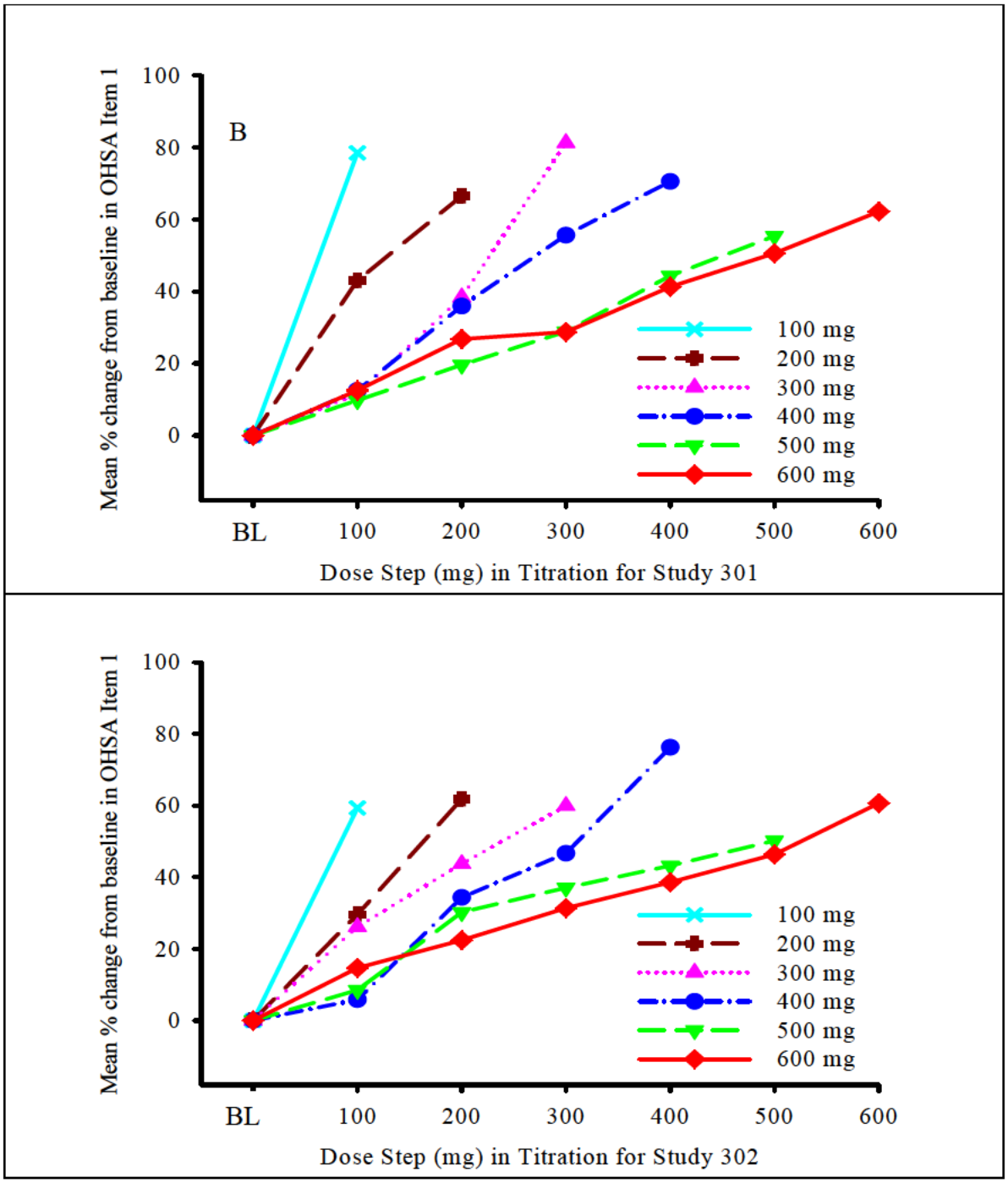

Figure 1. Mean % change from baseline in OHSA Item 1 during the open-label dose titration phase in (A) study 302 and (B) study 301. Each line represents a maintenance dose group as patients are titrated, starting with 100 mg TID on the first day to the maximum dose of 600 mg TID. BL stands for baseline measurement. A dose-dependent change in OHSA Item 1 is evident within each maintenance dose group.

Reference ID: 3076920

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/s/

SREEDHARAN N SABARINATH
01/25/2012

FANG LI
01/25/2012

PRAVIN R JADHAV
01/25/2012

RAJANIKANTH MADABUSHI
01/25/2012

MEHUL U MEHTA
01/25/2012

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	203-202 (N-000)
Submission Date:	09/23/11, 01/05/12
Brand Name:	Northera
Generic Name:	Droxidopa
Formulation:	Immediate release (IR) capsules
Strength:	100, 200, and 300 mg
Applicant:	Chelsea
Type of submission:	Original, Priority (6 months)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Droxidopa is reportedly an orally administered, synthetic catecholamine acid pro-drug. It has been approved in Japan since 1989 for the treatment of OH (orthostatic hypotension), syncope, and dizziness on standing up in Familial Amyloid Polyneuropathy (FAP) and Shy-Drager Syndrome, and for the treatment of freezing phenomenon and dizziness on standing up in PD (Parkinson's disease).

Current Submission

Droxidopa is being developed by Chelsea for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure in the US. On 09/23//11, Chelsea submitted NDA 203-202 (N-000) for Northera 100, 200, and 300 mg IR capsules. It was designated for a priority review (6 months).

Biopharmaceutics Review

(b) (4)

The 100 and 200 mg IR capsules that were tested in the phase III clinical trials have the same formulations as the commercial ones. The 300 mg strength/formulation has not been tested clinically.

A bioequivalence (BE) study was conducted to link the 300 mg and the clinically tested 100 mg capsules. The pharmacokinetic (PK) information on the 200 mg strength was obtained from the population PK (PPK) approach with sparse sampling technique in patients enrolled in the Phase III trials. Therefore, there is no biowaiver issue. The CMC information is currently under review by the chemist and the dissolution information is reviewed here.

Biopharmaceutics review focused on the dissolution development report, proposed dissolution methodology and the dissolution acceptance criterion for Northera capsules. The proposed dissolution method and the revised acceptance criterion as shown below are acceptable.

USP Apparatus:	**1 (Basket) with 100 rpm**
Medium:	**0.1N HCl, 900 mL at 37°C**
Acceptance Criterion:	**Q= (b) (4) at 20 min**

Reference ID: 3071691

RECOMMENDATION
From the Biopharmaceutics perspective, this NDA is acceptable.

_____ 01/06/12

Tien-Mien Chen, Ph.D. Date
ONDQA Biopharmaceutics Reviewer

_____ 01/06/12

Tapash Ghosh, Ph.D. Date
ONDQA Biopharmaceutics Acting Team Leader

CC: NDA, Tien-Mien Chen

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

NOH occurs in patients with a variety of neurodegenerative and congenital neurological disorders and is characterized by a reduction in SBP of at least 20 mmHg or DBP of 10 mmHg, but minimal change in heart rate, within 3 minutes of standing. These conditions are associated with an inadequate norepinephrine (NE) response from sympathetic vasomotor neurons, resulting in autonomic failure and generalized BP dysregulation. In patients with neurodegenerative or congenital neurological diseases, NOH is caused by inadequate release, or utilization of NE from sympathetic vasomotor neurons, leading to vasoconstrictor failure in response to standing.

Droxidopa is reportedly an orally administered, synthetic catecholamine acid pro-drug that is converted to NE through a single step of decarboxylation by an enzyme found in many tissues including autonomic nerve terminals. Droxidopa was approved in Japan in 1989 for the treatment of OH, syncope, and dizziness on standing up, and for the treatment of freezing phenomenon and dizziness on standing up in PD. Droxidopa is being developed by Chelsea for the treatment of symptomatic NOH in patients with primary autonomic failure in the US.

CURRENT SUBMISSION

On 09/23//11, Chelsea submitted NDA 203-202 for Northera 100, 200, and 300 mg IR capsules. It was designated for a priority review (6 months).

BIOPHARMACEUTICS REVIEW

The 100 and 200 mg IR capsules tested in the phase III clinical trials have the same formulations as the commercial ones. The 300 mg strength/formulation has not been tested clinically. A bioequivalence (BE) study was conducted, a randomized, open-label, single-dose, 2x2 crossover, PK study in healthy male and female volunteers. The PK information on the 200 mg strength was obtained using the PPK approach with sparse sampling technique in patients enrolled in the Phase III trials. Therefore, there is no biowaiver issue. The CMC information is currently under review by the chemist and the dissolution information is reviewed here.

FORMULATION COMPARISONS

The composition and formulation of the proposed commercial Northera IR Caps are shown below. (b) (4)

Reference ID: 3071691

Table 1. Composition and Formulation of the Proposed Commercial Northera IR Capsules 100, 200, and 300 mg

Ingredient	Function	100 mg Capsule		200 mg Capsule		300 mg Capsule	
		mg/Capsule	Percent w/w	mg/Capsule	Percent w/w	mg/Capsule	Percent w/w
Droxidopa	Active	100	(b) (4)	200	(b) (4)	300	(b) (4)
Mannitol, USP/Ph. Eur.							(b) (4)
Corn starch, NF/Ph. Eur./JP							
Magnesium Stearate, NF/Ph. Eur.							
Total Weight		270 mg	100.0	370 mg	100.0	480 mg	100.0
Empty Capsule[a]	Encapsulation	Size 3		Size 2		Size 1	

[a] = Size 3 capsules are light blue/white opaque, Size 2 capsules are light yellow/white opaque and, Size 1 are light green/white opaque. The capsules will be imprinted with (b) (4) black ink.

The commercial batch size will be (b) (4) capsules for the 100 mg strength (b) (4) capsules for the 200 mg strength (b) (4) and (b) (4) capsules for the 300 mg strength (b) (4)

The NDA registration batches were manufactured with at least 1/10 of the above full production batch sizes, at (b) (4) capsules (b) (4) capsules (b) (4) and (b) (4) capsules (b) (4) respectively.

DISSOLUTION METHODOLOGY AND SPECIFICATIONS

The solubility of droxidopa is shown below:

Aqueous Solubility at 20°C:

0.1mol/L HCl: (b) (4)

Water:

pH 3.0 McIlvaine buffer:

pH 4.0 McIlvaine buffer:

pH 5.0 McIlvaine buffer:

pH 6.8 phosphate buffer:

The following dissolution conditions were explored:

(b) (4)

The applicant submitted the dissolution development report. Please see the summary of the dissolution development report in Appendix 1 for details. The above report and the following proposed dissolution method were reviewed and found acceptable.

USP Apparatus: **1 (Basket) with 100 rpm**
Medium: **0.1N HCl, 900 mL at 37ºC**

The dissolution profile data of the three stability batches are shown below:

Figure 1. Comparative Dissolution Data of Northera (Droxidopa) 100 mg Capsules

(b) (4)

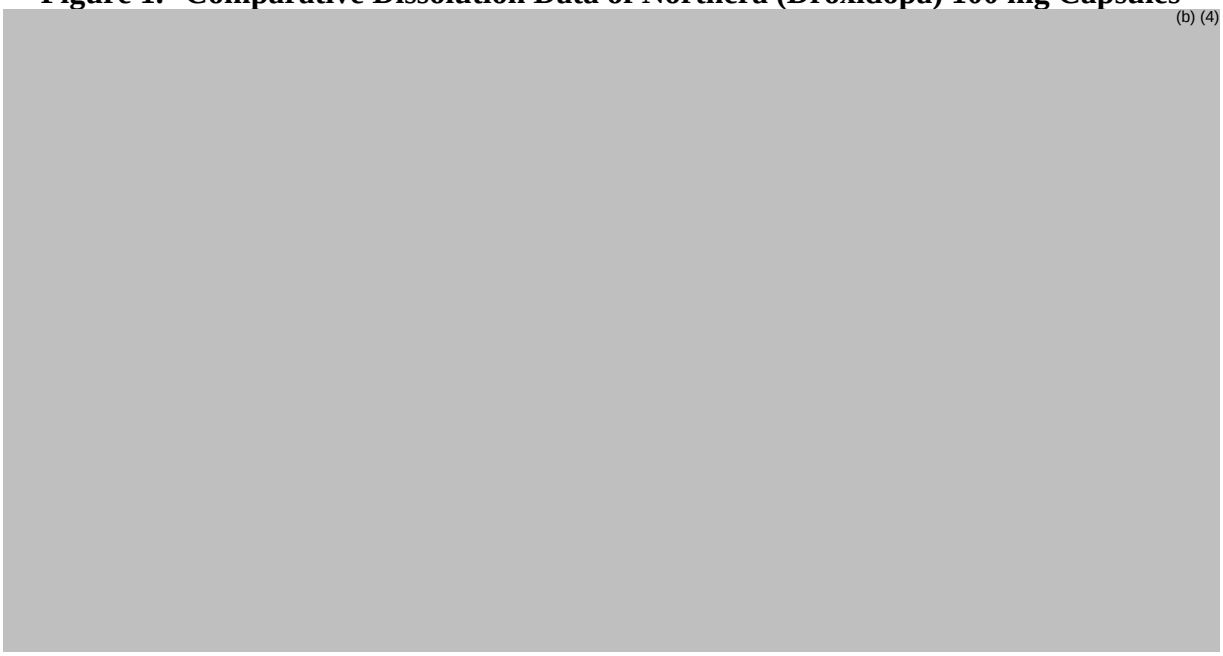

Figure 2. Comparative Dissolution Data of Northera (Droxidopa) 200 mg Capsules

(b) (4)

Figure 3. Comparative Dissolution Data of Northera (Droxidopa) 300 mg Capsules

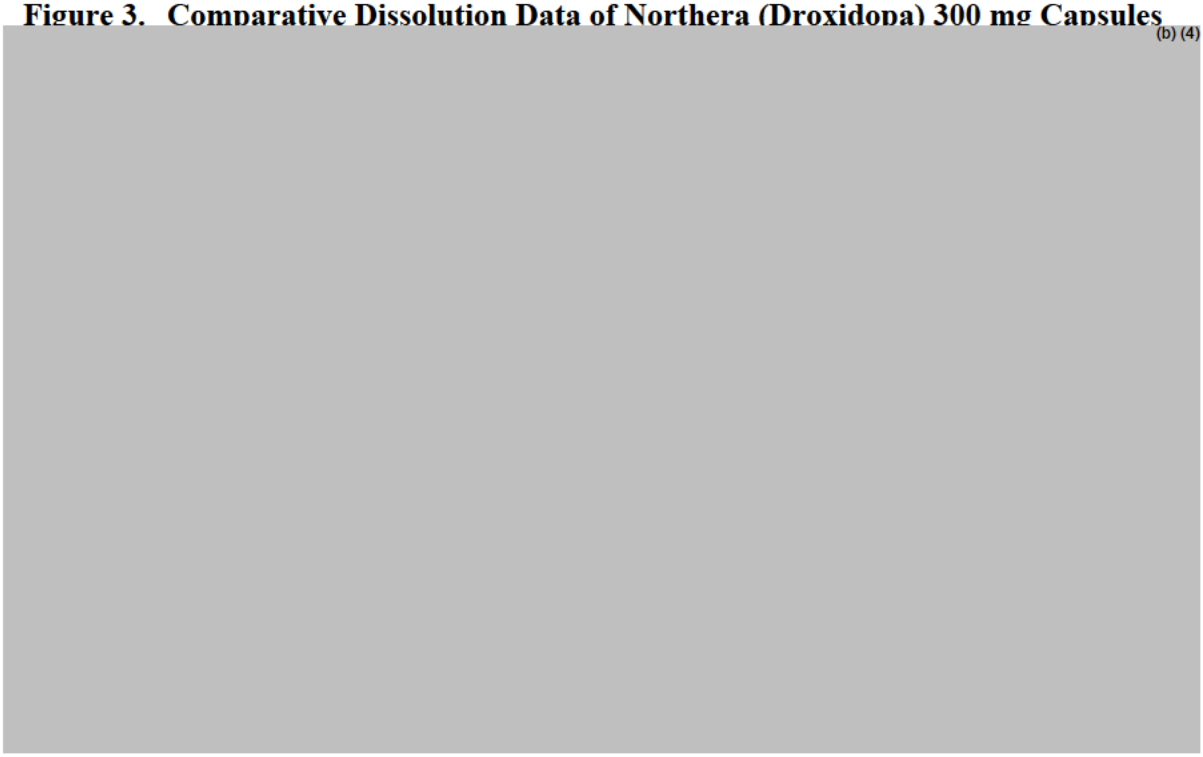

Table 2. Batch Nos. and Mean Dissolution Data of Clinical and/or Stability Batches

100 mg: Time	Batch #	0	10	20	30	45	60	Infinity
(b) (4)								

200 mg: Time	Batch #	0	10	20	30	45	60	Infinity
(b) (4)								

300 mg: Time	Batch #	0	10	20	30	45	60	Infinity
(b) (4)								

Note:
The drug substance was initially manufactured using the (b) (4) method by (b) (4) (b) (4) and per request by the Agency, the (b) (4) method was switched to (b) (4) method (b) (4) The drug substance manufactured using (b) (4) method was also obtained from another manufacturer. (b) (4)

The applicant proposed dissolution acceptance criterion as shown below.

Acceptance criterion: Q=(b) (4) at (b) (4)

The capsules all dissolved (b) (4) i.e., a mean of (b) (4) (b) (4) minutes. Therefore, the proposed dissolution acceptance criterion, Q=(b) (4) at 30 minutes needs to be (b) (4) to Q=(b) (4) (b) (4) minutes. The batches stored for long-term stability up to 24 months (25ºC/60% RH) also showed (b) (4) at 20 minutes (Module 32P83) supporting a (b) (4) dissolution acceptance criterion of Q=(b) (4) at 20 minutes.

An information request to (b) (4) the dissolution acceptance criterion was sent to the applicant on 12/22/11. On 01/05/12, the applicant agreed with the Agency's proposal and submitted the revised dissolution acceptance criterion of Q=(b) (4) at 20 minutes to update the Module 32P51. Specifications.

Reviewer's Comments:

1. The stability batches manufactured were pilot batches, but were >1/10 of the full production ones. The ONDQA (Office of New Drug Quality Assessment) considers that this is acceptable.

2. The above dissolution data showed comparable *in vitro* dissolution results among the drug product using the drug substance manufactured by three different methods. It is also true among three strengths.

3. The sponsor should have evaluated discriminatory ability of the method further to make future changes.

NDA 203-202 (N-000) for Northera (Droxidopa) IR Capsules, 100, 200, and 300 mg

Appendix 1

Summary of Dissolution Development Report

3 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

NDA 203-202 (N-000) for Northera (Droxidopa)
IR Capsules, 100, 200, and 300 mg

Appendix 2

Batch Information

Reference ID: 3071691

Table 1-1. Batch Information on Northera 100 mg IR Capsules

Batch No:	Strength:	Date of Manufacture:	Batch Size:	Drug Substance Manufacturer/ Drug Substance Lot:	Use:
C7E0233	100 mg	29 May 2007		(b) (4)	Phase III Clinical/ NDA Stability
C7E0234	100 mg	30 May 2007			Phase III Clinical/ NDA Stability
C7E0235	100 mg	01 Jun 2007			Phase III Clinical/ NDA Stability
C7J0058	100 mg	24 Oct 2007			Phase III Clinical
C8I0115	100 mg	15 Sep 2008			Phase III Clinical
C9B2023	100 mg	04 Feb 2009			Phase III Clinical
C9D2294	100 mg	03 Jun 2009			Phase III Clinical
C9F2113	100 mg	11 Jun 2009			Development/ NDA Stability
C9F2116	100 mg	24 Jun 2009			Development/ NDA Stability
HYG	100 mg	25 Nov 2009			Phase III Clinical
TSY	100 mg	23 Feb 2010			Phase III Clinical
CDND	100 mg	27 Apr 2010			Phase III Clinical
CMFZ	100 mg	22 Jul 2010			Phase III Clinical

Table 1-2. Batch Information on Northera 200 mg IR Capsules

Batch No:	Strength:	Date of Manufacture:	Batch Size:	Drug Substance Manufacturer/ Drug Substance Lot:	Use:
C7E0236	200 mg	30 May 2007		(b) (4)	Phase III Clinical/ NDA Stability
C7E0239	200 mg	30 May 2007			Phase III Clinical/ NDA Stability
C7E0241	200 mg	01 Jun 2007			Phase III Clinical/ NDA Stability
C7J0059	200 mg	25 Oct 2007			Phase III Clinical
C8C0040	200 mg	19 Mar 2008			Phase III Clinical
C8I0108	200 mg	16 Sep 2008			Phase III Clinical
C9B2025	200 mg	05 Feb 2009			Phase III Clinical
C9D2295	200 mg	03 Jun 2009			Phase III Clinical
C9F2114	200 mg	11 Jun 2009			Development/ NDA Stability
C9F2117	200 mg	26 Jun 2009			Development/ NDA Stability
HYH	200 mg	26 Nov 2009			Phase III Clinical
CMGB	200 mg	22 Jul 2010			Phase III Clinical
VDB	200 mg	23 Feb 2010			Phase III Clinical
CDNF	200 mg	27 Apr 2010			Phase III Clinical
DGGC	200 mg	19 Nov 2010			Phase III Clinical
DKPD	200 mg	02 Dec 2010			Phase III Clinical

Table 1-2. Batch Information on Northera 300 mg IR Capsules

Batch No:	Strength:	Date of Manufacture:	Batch Size:	Drug Substance Manufacturer/ Drug Substance Lot:	Use:
C8D0311	300 mg	05 May 2008		(b) (4)	NDA Stability
C8D0312	300 mg	07 May 2008			NDA Stability
C8D0313	300 mg	08 May 2008			Phase I Bioequivalence/ NDA Stability
C9F2115	300 mg	11 Jun 2009			Development/ NDA Stability

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIEN MIEN CHEN
01/13/2012

TAPASH K GHOSH
01/13/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

Droxidopa is an orally bioavailable, synthetic catecholamine acid pro-drug that is converted to norepinephrine (NE) through a single step decarboxylation by endogenous DOPA decaroxylase enzyme. The sponsor is seeking approval for droxidopa for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure, dopamine beta hydroxylase deficiency and non-diabetic autonomic neuropathy.

Droxidopa capsules are formulated in 3 strengths: 100, 200 and 300 mg. The 100 and 200 mg capsules were used in the phase III trials.

Bioequivalence is demonstrated between 3 x 100 mg and 1 x 300 mg capsules in a dedicated study.

The efficacy findings for droxidopa are derived from two phase III studies: one pivotal study (Study # 301) and one supportive study (Study # 302). In addition the sponsor has submitted one 24 hour ambulatory BP study (Study # 305) and a long term safety and efficacy study (Study # 303) as supportive evidence.

Droxidopa is shown to have low CYP induction or inhibition potential *in vitro* and there are no dedicated drug-drug interaction studies as part of the current submission. The phase III trials included patients with mild/moderate renal impairment and the current NDA has no separate renal/hepatic impairment studies.

	Information		Information
NDA/BLA Number	**203202**	**Brand Name**	**NORTHERA**
OCP Division	**I**	**Generic Name**	**droxidopa**
Medical Division	**DCRP**	**Drug Class**	**Pro-drug for Norepinephrine (NE)**
OCP Reviewer	**Sreedharan Sabarinath**	**Indication**	**Symptomatic neurogenic orthostatic hypotension (NOH)**
OCP Team Leader	**Rajanikanth Madabushi**	**Dosage Form**	**Capsules**
Pharmacometrics Reviewer	**Sreedharan Sabarinath**	**Dosing Regimen**	**Three times daily**
Pharmacometrics Team Leader	**Pravin Jadhav**	**Route of Administration**	**Oral**
Date of Submission	**09/28/2011**	**Sponsor**	**Chelsea Therapeutics, Inc**
Estimated Due Date of OCP Review	**1/28/2012**	**Priority Classification**	**Priority**
Medical Division Due Date	**TBD**		
PDUFA Due Date	**03/28/2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies to be reviewed**	**Critical Comments If any**
`STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			

1 File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**2**	**2**	**Two bioanalytical methods for Droxidopa, 3-OM DOPS and Norepinephrine were used for clinical studies**
I. Clinical Pharmacology				
Metabolism:	**X**	**2**	**2**	**Study E-01 clinical PK and metabolism study, Study D-08 urine analyses for 300 mg dose**
Mass balance:				
Isozyme characterization:	**X**			**Enzyme induction study, Enzyme inhibition study**
Blood/plasma ratio:				
Plasma protein binding:	**X**	**2**	**2**	**Study D-07, study IB-3**
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**4**	**4**	Study 20/1859-94 (100 – 900 mg) Study 20/1860-94 (100 – 600 mg) **Studies 101 and 102 (QTc) with final US marketing formulation in healthy elderly**
multiple dose:	**X**	**1**		**Study 101 (part 1 is the single dose)**
Patients-				
single dose:				
multiple dose:	**X**	**1**		**Phase 3 Study 302 (POPPK)**
Dose proportionality -				
Fasting single dose:	**X**			**Study 101 (3 x 100 mg Vs 1 x 300 mg)**
fasting / non-fasting multiple dose:	**X**			**Study 101**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vitro:	**X**	**2**	**2**	**Enzyme induction study, Enzyme inhibition study**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**6**	**6**	**Study S10002 and its extension S10002a for safety, study 2034 and its extension study 2175, study 2062 and its extension 2210**
Phase 3:	**X**	**4**	**4**	**Studies 301, 302, 303, 305**
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**			**Study S10002 and its extension S10002a for safety, study 2034 and its extension study 2175, study 2062 and its extension 2210**
Phase 3 clinical trial:	**X**			**Studies 301, 302, 303, 305**
Population Analyses -				
Data rich:	**X**	**3**		**Using data from 3 phase 1 studies**
Data sparse:	**X**	**1**		**Phase 3 study 302 – to explore effect of covariates**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	**X**			
solution as reference:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

alternate formulation as reference:	X	1	1	Study D09, 100mg capsule, 200 mg capsule, (b) (4) (not FMI)
Bioequivalence studies -				
traditional design; single dose:	X			**Study 101**
replicate design; single dose:				
Food-drug interaction studies	X			**High fat meal, healthy elderly subjects, 3x100 mg vs 1x300 mg capsules**
Bio-waiver request based on BCS				**No Biowaivers requested**
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				**IR formulation**
III. Other CPB Studies				**None**
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies (completed)		**29***	**23**	**23 studies are identified for review**
(ongoing)		**2**		**Long term safety (304 and 306)**

*Some studies appear in multiple sections above.

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			100 mg and 200 mg FMI strengths were used in Phase 3 trials. 300 mg FMI strength demonstrated BE to 3 x 100 mg but in Phase 3, 100 + 200 mg was used. (b) (4) .
2	Has the applicant provided metabolism and drug-drug interaction information?	X			In vitro studies showed low induction or inhibition potential.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	Titrated to effect
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

3 File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			Titrated to effect
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		No ER analyses performed. Need for ER analyses will be determined at the Scoping Meeting
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

We have already communicated the following information request to sponsor through the project manger.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Please submit the following datasets to support the Pop-PK and PK/PD analysis:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any data point and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets. The flag of exclusion should be clearly explained in the define.pdf file.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- If applicable, a model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

We will contact the sponsor through the project manager if any additional review issues come up during the review process.

Sreedharan Sabarinath	10/27/2011
Reviewing Clinical Pharmacologist	Date
Rajanikanth Madabushi	10/27/2011
Team Leader/Supervisor	Date

Reference ID: 3035644

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SREEDHARAN N SABARINATH
10/27/2011

RAJANIKANTH MADABUSHI
10/27/2011